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Increase in Guanidine-like Substance in Acute Liver Injury and Eclampsia.*

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A recent publication from this laboratory[1] reported an increase in guanidine or guanidine-like substances in the blood of dogs during the intoxication produced by carbon tetrachloride and chloroform. The increase in guanidine was soon followed by a marked fall in blood sugar which often reached levels of extreme hypoglycemia. Aside from these changes and a retention of bile pigments no marked abnormalities were noted in the blood chemistry. These intoxications were further characterized by nervous hyperexcitability followed by depression, and a gastro-intestinal irritation evidenced by vomiting, diarrhea, and frequent hemorrhages. The highly protective action of calcium salts in preventing and treating these intoxications has also been emphasized.[1, 2, 3]

The outstanding pathological change produced by chloroform and by carbon tetrachloride, which was the drug chiefly studied, is a severe central necrosis of the liver. Although no definite relationship between the increase in guanidine and the liver damage has yet been demonstrated, it is natural to associate, at least tentatively, the disturbed metabolism with so conspicuous an injury. With this hypothesis in mind, it seems probable that when similar liver injury has been caused in some way other than by the administration of these drugs, similar abnormalities and symptoms may be looked for, and if present might also be relieved by calcium therapy.

Studies of an introductory nature have been made of the blood chemistry with special reference to guanidine and blood sugar levels in a few clinical cases representing various types of liver disease and also in cases of eclampsia—a condition which the majority of observers believe is accompanied by pathological changes in the liver.[4]

* This investigation is one of a series of studies being made under the direction of Dr. P. D. Lamson on the pharmacology and toxicology of carbon tetrachloride. The work is being carried on with the support of the International Health Board.

[1] Minot, A. S., and Cutler, J. T., *J. Clin. Invest.*, 1928, vi, 369.

[2] Minot, A. S., and Cutler, J. T., PROC. SOC. EXP. BIOL. AND MED., 1928, xxvi, 138.

[3] Minot, A. S., PROC. SOC. EXP. BIOL. AND MED., 1927, xxiv, 617,

[4] Stander, H. J., *Medicine*, 1929, viii, 1.

Studies in Cases of Liver Disease. The guanidine was determined by the method of Major and Weber,[5, 6] taking into consideration the possibility of interference due to creatine. The non-protein nitrogen constituents, except uric acid, were determined by the methods of Folin and Wu,[7] uric acid and blood sugar by Benedict's methods.[8, 9]

In 5 cases of chronic liver disease including carcinoma of liver, syphilitic hepatitis, an old alcoholic cirrhosis, and obstructive jaundice, no significant deviation from the normal level was found in any of the blood constituents studied. The cases are of course too few to justify any conclusion, but one would perhaps expect more readjustment to, and hence less metabolic disturbance from an injury developing over a period of months or years than to an equally severe damage produced in a short time. Some indication that this is true is furnished by positive findings in 2 more acute cases. One case was diagnosed as acute arsphenamine hepatitis or acute catarrhal jaundice. On admission this patient showed a fasting blood sugar of 50 mgm., with a moderately increased guanidine concentration. He was mentally depressed and confused. On a regime of oral calcium lactate administration and a diet without meat and high in carbohydrate the mental condition improved and the patient felt much better. The blood sugar level was promptly restored and maintained at a level between 90 and 100 mgm. As the liver condition improved the guanidine concentration gradually returned to normal and calcium administration was no longer necessary to maintain the blood sugar level.

Similar results were obtained temporarily in an infant with congenital abnormality of the liver. No bile entered the intestine except at rare intervals despite the fact that the ducts were patent. Pathological studies after death showed a badly necrosed liver. On admission the baby was markedly jaundiced and showed typical symptoms of tetany. The blood sugar was 57 mgm. and the guanidine concentration about twice the normal level. Oral glucose administration together with the usual diet failed to raise the blood sugar above 70 mgm., but when calcium lactate was also given the blood sugar was maintained between 80 and 90 mgm. for a period of 2 or 3 weeks and the tetanic symptoms disappeared entirely.

[5] Major, R. H., and Weber, C. J., *Johns Hop. Hosp. Bull.*, 1927, xl, 87.

[6] Major, R. H., and Weber, C. J., *Arch. Int. Med.*, 1927, xl, 891.

[7] Folin, O., and Wu, H., *J. Biol. Chem.*, 1919, xxxviii, 81.

[8] Benedict, S. R., *J. Biol. Chem.*, 1922, lxi, 187.

[9] Benedict, S. R., *J. Biol. Chem.*, 1926, lxviii, 759.

During this time the calcium medication was withheld experimentally for a few days and the blood sugar promptly fell off but was restored again when medication was resumed. The jaundice and digestive disturbances secondary to the lack of bile in the intestine grew progressively worse until the baby finally died.

Cases of Pre-eclamptic Toxemia and Eclampsia. Ignoring for the moment the controversies which exist regarding what factors in the abnormalities seen in eclampsia are causes and what are effects of the toxic condition, and looking superficially at the clinical picture, one is impressed with the many points of similarity in this condition and in the intoxication seen in dogs with acute liver injury. The 2 conditions have in common a more or less acute liver injury, gastro-intestinal irritation, nervous disturbances, and, as reported by Titus, Dodds, and Willets,[10] a tendency toward hypoglycemia.

Careful studies of the blood chemistry have been carried out on 8 cases diagnosed as pre-eclamptic toxemia, 4 cases of real eclampsia with convulsions, 1 case of pregnancy complicated by chronic nephritis, 1 case of pneumonia in a woman in the sixth month of pregnancy, and less complete studies on several dispensary cases of persistent vomiting of pregnancy. Several cases of normal pregnancy were also studied. Aside from the well recognized[4] tendency for the uric acid concentration in the blood to run higher than normal, the usual non-protein nitrogen constituents were found to be normal in the pre-eclamptic and eclamptic cases. The fasting blood sugar levels were definitely decreased in the pre-eclamptic toxemias—ranging between 60 and 75 mgm., as compared to concentrations of from 90 to 105 in cases of normal pregnancy. The tendency to hypoglycemia was even more marked in true eclampsia especially just before a convulsive seizure when in 2 cases blood sugar concentrations of 37 and 52 mgm. respectively were found. The guanidine concentrations were also definitely abnormal in both of the groups mentioned—values between 0.50 and 0.85 mgm. being usually obtained as compared to the normal values of from 0.25 to 0.40 mgm. per 100 cc. of blood. No abnormalities in the blood sugar or guanidine concentrations were found in the cases of pregnancy complicated by nephritis or pneumonia.

Three pre-eclamptic cases entered the hospital and were given calcium medication while the blood chemistry was carefully followed. Very promptly (within 1-2 hours) after the intravenous administration of calcium in the form of 10 cc. of a 10% calcium

[10] Titus, P., Dodds, P., and Willets, E. W., *Am. J. Obs. and Gyn.*, 1927, xiv, 89.

gluconate solution (Sandoz Co.'s sterile ampoules) and within 24 hours after the oral administration of either calcium gluconate or lactate was started the lowered blood sugar levels were restored to within the limits of 90 to 100 mgm. per 100 cc. of blood. Accompanying this change there was a general amelioration of symptoms, less nausea, and a considerable fall in blood pressure. The guanidine concentration was unaffected by medication. All 3 patients gave birth to living normal infants. Soon after delivery the guanidine concentrations returned to normal and calcium medication was no longer necessary to maintain a normal blood sugar level. Several other dispensary patients in the pre-natal clinic showed similar symptomatic improvement after calcium medication but no blood chemical studies were made.

More striking results were obtained in a case of eclampsia with convulsions given intravenous calcium medication. This patient suddenly became blind, showed tetanic symptoms, and was nearly unconscious. The blood sugar concentration was 52 mgm. and the guanidine 0.64 mgm. per 100 cc. of blood. A dose of 10 cc. of 10% calcium gluconate was given by vein. Within 15 minutes the vision was much improved and the mental condition more alert. Forty minutes after the dose the blood sugar was increased to 76 mgm. and the sight normal and the patient rational but weak. This improvement persisted for several hours. About 6 hours later it was decided to induce labor and glucose was given intravenously to improve the patient's strength. During labor, which was very long and difficult, the patient suffered a relapse into blindness and the same convulsive condition but again promptly responded symptomatically to intravenous calcium therapy. The baby was still-born. The mother survived and showed no further tendency to hypoglycemia or convulsive symptoms after delivery but died 3 weeks later from a local infection complicated with extreme anemia.

Although the number of cases studied is small, we believe that the data obtained indicate that in certain clinical types of liver disease and in eclampsia the same abnormalities in blood chemistry are present as were seen in dogs during the intoxication produced by carbon tetrachloride or chloroform. Calcium medication has furnished prompt relief in a few clinical cases showing increased guanidine and low blood sugar concentration. It is hoped that further work along these lines in laboratories where larger amounts of clinical material are available may further evaluate these findings.

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Skin Reactions to Pollen and to Histamine.

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Certain "allergic" patients are classed as non-sensitive because no skin reactions are obtained when they are tested with the usual allergens. It is important to know if a direct relationship exists between reaction capacity and the type of skin under study, or if the site of the test is an important factor. The work of Lewis[1] and his associates has furnished us a method for studying reaction capacity in the skin hypersensitive or non-sensitive individual.

Histamine, in the following dilutions, 1-1,000; 1-10,000; and 1-100,000 (of the base) was employed as a test substance for both types of patients. Similar dilutions of pollen extracts were tested on those who were pollen sensitive. All tests were intracutaneous, and were made in the long axis on the flexor surface of the forearm. The amount injected, usually 0.01 cc., produced a welt 1.0 to 1.5 mm. in diameter. Beginning at the antecubital space the first welt was made with the 1-1,000 dilution of the test substance. The 1-100,000 was the most distal. At the wrist the opposite margin of the arm was employed and the tests were in the reverse order—the 1-1,000 was most distal. The tests were repeated 3 times using alternate arms. The wheal, the area of "reflex arteriolar dilatation",[1]—secondary erythema—was measured and the presence of pseudopods noted. The patients included some with an elastic and others with a senile or crepe-paper type of skin. Some were taking epinephrin frequently, others had never employed the drug.

The senile, atrophic, "crepe-paper" type of skin may give as large a reaction to histamine, or to pollen if the patient is sensitive, as is given by an elastic skin. The variation from patient to patient is characteristic of the individual and seemed to be unrelated to the type of skin. There were many instances where a patient gave a

* With the technical assistance of Maurine Cannon, R. N.

[1] Lewis T., *et al.*, *Heart*, 1924, xi; 1926, xiii; 1927, xiv.