that HeLa cells adapted to growth in the presence of horse serum rather than in media containing human serum are quite susceptible to the cytopathogenic effect of all three types of poliomyelitis virus, and are as efficient in producing virus as the HeLa cells grown in the human serum. They likewise seem to be as efficient in their ability to demonstrate the presence of poliomyelitis virus in human stool suspensions. Preliminary evidence indicates that this subline of HeLa cell grown in mass suspended cultures is also capable of supporting the growth of poliomyelitis virus.

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Received July 28, 1955. P.S.E.B.M., 1955, v90.

Glycemic Effects of Chlorpromazine in the Mouse, Hamster and Rat. (21947)

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Various pharmacological effects of chlorpromazine (CPZ) have been reported in the literature among which are depression of body temperature, potentiation of morphine and barbiturates, anti-epinephrine as well as anti-acetylcholine action, and a depression of cellular activity or narcobiosis(1,2,3). The drug which structurally is 10-(3-dimethylaminopropyl)-2-chlorophenothiazine hydrochloride is similar in structure to promethazine but shows very little anti-histaminic property. In view of the various profound effects on the nervous system and cellular activity, the question arose as to the possible effects on blood sugar levels during the post-injection period when this substance is pharmacologically most active.

Materials and methods. The effect of intraperitoneal injections of chlorpromazine (Thorazine, S.K.F.) on blood sugar level of non-fasted and fasted white male mice of the Rockland (RAP) strain was first studied. Animals were injected with CPZ at 5 mg/kg body weight and blood samples were withdrawn *via* the orbital sinus(4), at intervals of 30 minutes, and at 1, 2, 3 and 5 hours later. Non-injected controls were bled at the same interval periods and blood sugar determinations similarly made. Since the response to CPZ injection in mice was a substantial wave of hyperglycemia, similar experiments were carried out with the hamster and rat. Also the glycemic effects of chlorpromazine in the alloxan diabetic mouse, and the effects, if any, of this substance on the hypoglycemic action of insulin were observed. Mice were separated into 2 groups, each group consisting of 16 animals. Group I was made diabetic by subjecting it to a 48-hour fasting period followed by injection of alloxan monohydrate, 75 mg/kg *via* the intracardiac route(5). After diabetes had been established, these animals were treated with CPZ and the glycemic effects determined. Group II mice received insulin injections in the following manner: Animals were fasted for 24 hours, injected with CPZ, 5 mg/kg, ip, and 2 hours later were injected subcutaneously with insulin, 1/6 unit per 18 g body weight. A minimum of 16 animals was used in all cases for each type of experiment with mice, hamsters and rats. Blood sugar determinations were made by the Somogyi-Nelson method(6).

Results. Normal male mice receiving CPZ

injections of 5 mg/kg, ip, showed an average progressive increase in blood sugar from 142.2 to 202.3 mg% in 30 minutes which by 3 hours had reached 282.8 mg%. A gradual decline in blood sugar then followed which at 5 hours post-injection time had returned to slightly higher than normal value. Non-treated animals which were bled at the same time intervals as treated ones showed a slight blood sugar elevation at the end of the first hour, but all succeeding blood sugar samples were within the normal range.

The hamster showed a hyperglycemic response to CPZ injections similar to that obtained in the mouse although to a lesser degree. The minimal dose required to produce a significant hyperglycemic response was found to be 10 mg/kg when injected intraperitoneally. Hamsters in both the fasted and non-fasted state showed an elevated blood sugar level following CPZ injection, but the hyperglycemia was more pronounced in those animals which had not been starved. The average 24-hour fasting blood sugar level was found to be 96 mg% and 3 hours after injection of CPZ at 10 mg/kg, ip, the glycemic level was raised to 194 mg%. The non-fasted hamster had a glycemic level of 108 mg% which reached 212 mg% at 3 hours after injection of CPZ.

The rat showed very little if any significant rise in blood sugar following injections of CPZ. Various doses were tried ranging from 5 to 60 mg/kg, the latter being approximately the LD_{50}, and in each case the blood sugar level was not appreciably changed. The average fasting glycemia level in the rat was found to be 89 mg% and the maximal glycemic response produced by any dose level was an elevation to 127 mg%. This occurred at 3½ hours following ip injection of CPZ at 20 mg/kg of rat body weight.

Chlorpromazine intensified the fasting hyperglycemia in alloxan diabetic mice and significantly decreased the survival time of these diabetic animals. The average 24-hour fasting blood sugar in the non-treated diabetic mice was 374 mg% while those treated with CPZ showed an elevation to greater than 600 mg% at 2 hours post-injection time. Blood samples were taken in all diabetic mice on alternate days via cardiac puncture with none of the 16 diabetic mice receiving CPZ at 5 mg/kg surviving more than 3 days after such treatment. In contrast to this, 60% of the non-treated alloxan diabetic animals survived a week of alternate day blood withdrawals. In practically all cases of treated and non-treated animals death occurred during the 24-hour starvation period prior to blood sampling. All blood samples were collected in amounts not exceeding 0.2 ml.

Chlorpromazine was observed to afford some protection against the hypoglycemic convulsions and subsequent death produced in mice by injection of 1/6 unit of insulin per 18 g body weight. Of the 16 mice which received insulin at 2 hours after injection of CPZ, 9 animals exhibited convulsions but no deaths occurred in spite of the fact that no glucose was administered. Of the 16 mice receiving the same dose of insulin but no CPZ, 14 convulsed and 11 of these died.

Discussion. It is of interest to speculate on the means by which chlorpromazine brings about so significant a rise in glycemic levels of the mouse and hamster. First, of course, would be the narcobiotic action of this substance which decreases cellular activity so that metabolic oxidation reactions are depressed. This would in effect decrease the amount of glucose being oxidized within the cell and therefore decrease the need or intake of glucose by the cell from extracellular spaces and the blood. As a consequence a rise in blood sugar would occur. Whether or not the depression of cellular activity is the sole means by which CPZ brings about its hyperglycemic effect is difficult to say at this time. The hypothermic effect of this drug, which might be used as an index of cellular activity, is also produced in the rat and yet this animal shows no appreciable hyperglycemic response. The possibility of the endocrine glands such as the adrenals, hypophysis or pancreas acting directly or indirectly through glycogenolysis or gluconeogenesis in the liver has yet to be explored. The profound species variation between the rat and the mouse in the hyperglycemic response to this drug cannot be fully explained at this time. The basal metabolic rate is appreciably higher in the mouse(7).

and this may be the requisite for demonstrating a hyperglycemic response to CPZ since a depression of cellular metabolism in an animal normally functioning at a high metabolic rate would bring about more pronounced changes in the concentration of substances in the blood which are metabolized than would be expected in an animal with a lower normal rate of metabolic activity. Evidence in support of this concept would be the somewhat intermediate effect of CPZ on the blood sugar of the hamster which has a BMR somewhat intermediate to that of the mouse and rat (8,9).

The protection afforded by CPZ from the hypoglycemic convulsions and death following insulin injection in mice would be expected in view of the hyperglycemic state of these animals prior to insulin administration. Whether or not there is any direct antagonism of the insulin molecule cannot be said without further investigation.

Summary. The glycemic effects of chlorpromazine were studied in the mouse, hamster and rat. A hyperglycemic response was found in the mouse and hamster with the mouse having the greater response of the two No significant glycemic change was observed in the rat. An exacerbation of the diabetic state and decrease in survival time was found in alloxan diabetic mice treated with CPZ. A protection from hypoglycemic convulsions and death produced by insulin was afforded to mice which had been injected with CPZ 2 hours previous to the injection of insulin.

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Received September 27, 1955. P.S.E.B.M., 1955, v90.

Induction of Toxigenicity in Non-Toxigenic Strains of *C. diphtheriae* with Bacteriophages Derived from Non-Toxigenic Strains. (21948)

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Freeman(1,2) reported that some bacteriophages isolated from *C. diphtheriae* could induce totally non-toxigenic strains of *C. diphtheriae* to become toxigenic and that these transformed strains were indistinguishable in all respects from toxigenic strains occurring in nature. This observation has been confirmed in this laboratory(3,4) as well as in other laboratories(5,6). In each instance, toxigenicity was induced only by bacteriophages obtained from naturally-occurring toxigenic strains of *C. diphtheriae*.

Because of the epidemiological significance of this transformation, studies were undertaken to determine the relative frequency with which the change could be produced in non-toxigenic strains isolated from cases and carriers. Of the 52 strains tested so far the change has been induced in only 8 strains, all of which were the mitis or mitis-like type. While Hewett(7) has reported the transformation in gravis-type strains employing phages derived from toxigenic gravis strains, it has not been accomplished in this laboratory. However, definitions of the gravis type differ in different laboratories. During serial passage of one group of cultures with phages from toxigenic strains, complete lysis was obtained with 2 non-toxigenic strains, (A-8888, mitis-like North Dakota, and A-8782, gravis,