GALACTOSE TOLERANCE OF NORMAL AND DIABETIC SUBJECTS, AND THE EFFECT OF INSULIN UPON GALACTOSE METABOLISM

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It is the purpose of this paper to present the results of an investigation of galactose metabolism by determining the galactose content of the blood and urine following the administration of galactose by mouth to human subjects, and by determining the galactose concentration of the blood following the subcutaneous, intravenous, or intraperitoneal administration of galactose to animals. Investigations of galactose metabolism by similar procedures have been carried out by Corley (1), Blanco (2), Harding and van Nostrand (3), and Harding and Grant (4).

The analytical method used to determine the blood galactose is an application of the procedure of Somogyi (5), in which the fermentable sugar of the blood is removed by treatment with yeast, and of the new Benedict (6) method for determining blood glucose in tungstomolybdic acid filtrates. The urinary galactose was determined by treating the urine with yeast for $\frac{1}{2}$ hour or more, centrifuging the mixture, and titrating the supernatant fluid against Benedict's quantitative copper reagent.

Method for Determination of Galactose in Blood

Pipette 1 cc. of blood into a small Erlenmeyer flask. Add 7 cc. of 10 per cent washed yeast suspension. Shake the flask to mix the contents thoroughly and place it in an incubator at 37–40° for 15 minutes. The flask should be shaken two or three times during the incubation period to bring about a resuspension of the yeast in the blood. After 15 minutes, remove the flask from the incubator and add 1 cc. of Benedict's tungstomolybdate solu-

tion (7). Add 1 cc. of 0.62 N sulfuric acid, mix thoroughly, and
filter through a filter paper which has previously been washed free
of soluble reducing substances. Pipette 2 cc. of the filtrate into a
Folin-Wu blood sugar tube. Two galactose standards are now
prepared. In one Folin-Wu tube place 1 cc. of standard galac-
tose solution containing 0.1 mg. of galactose per cc. and add 1 cc.
of distilled water. In another Folin-Wu tube place 2 cc. of the
standard galactose solution. To the two standard tubes and the
tube containing blood filtrate add 2 cc. of the Benedict copper
reagent (6). Place the tubes in a boiling water bath for 6 minutes.
Remove the tubes, cool, and add to each tube 2 cc. of the Benedict
phosphomolybdic acid color reagent (6). Shake the tubes vig-
orously until the contents are mixed, and dilute to 12.5 cc. Com-
pare the colored solutions in a colorimeter, with the galactose stand-
ard which most closely matches the unknown.

Calculation—The number of mg. of galactose per 100 cc. of
blood is equal to 1000 divided by the reading of the unknown if the
0.1 mg. galactose standard was used, or 2000 divided by the read-
ing of the unknown if the 0.2 mg. standard was used.

Reagents and Discussion of Method—The preparation of the
tungstomolybdate solution, the alkaline copper sulfate reagent,
and the phosphomolybdic acid reagent is described in the papers
by Benedict (6, 7). The yeast (Fleischmann's) is washed by sus-
pending in distilled water in centrifuge tubes, centrifuging, and
decanting the supernatant fluid as described by Somogyi (5); we
found three washings sufficient to remove the soluble reducing sub-
stances. Benedict (8) has called attention to the presence of
soluble reducing substances in different grades of filter paper. We
remove the soluble reducing substances from the filter paper used
in this method by washing with water. This is conveniently done
by placing the filters in a large beaker and covering them with
distilled water for 2 hours or more. The water is changed three
times during the washing and the filters are dried upon a rack.

The Benedict colorimetric procedure was adopted because of its
specificity for sugar in the presence of the non-sugar reducing sub-
stances of the blood, and also on account of the convenience and
practical adaptability of colorimetry to blood analysis. We
have tried the zinc and copper deproteinizing methods of Somogyi
(9, 10), but, in agreement with Benedict (6), we were not able to

get fermented filtrates free from non-sugar reducing substances when copper reduction methods of determination were used. We also were unable to get quantitative recoveries of galactose added to blood when the zinc deproteinizing method of Somogyi was used, the best recoveries obtained being 80 per cent of added galactose from blood deproteinized by zinc reagents which gave a filtrate with a pH of 7.5. Using the method described above, and deducting the saccharoid value determined by Benedict's (6) method, we obtained recoveries of galactose added to blood ranging from 98 to 108 per cent.

In preparing the standard galactose solution, a stock solution is first made by dissolving 1 gm. of c.p. galactose in 100 cc. of saturated benzoic acid solution. This stock solution is then diluted 100 times with saturated benzoic acid solution to obtain the standard used in blood analysis, which contains 0.1 mg. of galactose per cc. In the absence of adequate information upon the keeping qualities of this standard galactose solution we recommend at this writing that a fresh galactose standard be prepared once in 3 months. Galactose solutions prepared from c.p. Pfanstiehl galactose have 77 per cent of the reducing power of glucose of highest purity (United States Bureau of Standards).

With this method a plus value for galactose is obtained due to the presence of non-sugar reducing substances in blood. The non-sugar, or saccharoid, values of blood obtained by us varied from 4 to 11 mg. per 100 cc. as galactose. Benedict (6) has reported saccharoid values of 5 to 8 mg. per 100 cc. as glucose by his method. The values obtained by us, as galactose, correspond closely to the findings of Benedict, since galactose has only 77 per cent of the reducing power of glucose. One may obtain more specific values for blood galactose by determining the saccharoid content of a control sample of blood collected previous to the administration of galactose and subtracting this value from the results obtained upon blood samples collected later. This should give reliable results as the saccharoid content may not be expected to vary within a few hours. To determine the saccharoid content accurately, the procedure recommended by Benedict (6), in which a known amount of galactose is added to fermented filtrate, must be followed. In the experiments reported in this paper the saccharoid content of a control sample of blood was determined in all cases in

order that specific galactose values might be calculated, and also to have a constant check upon the activity of the yeast used. It makes no practical difference in interpretation of results, however, whether the blood galactose values obtained by this method are corrected for the saccharoid content, or are used uncorrected, since the saccharoid fraction of blood is fairly constant and falls within approximately 10 mg. per cent of the true value when this technique is used.

Experimental Procedure

Our experiments upon human subjects were conducted in the morning, the subjects having fasted since the night before, and no food was allowed during the period of the experiment. A control sample of blood was first obtained. The subjects were given by mouth galactose dissolved in a convenient quantity of water, which was from 300 to 500 cc. Samples of blood were then collected at $\frac{1}{2}$ hour, 1 hour, and 2 hour intervals following the ingestion of the sugar. The galactose content of the blood samples was determined by the method described above and the total blood sugar was estimated as glucose by the Benedict method (6). One urine sample was collected at the end of the 2 hour period. The galactose content of the urine of the normal subjects, and the amount of both galactose and glucose in the urines of the diabetic subjects, were determined. The amount of galactose given was 1 gm. per kilo of body weight. We believe that in a study in which conclusions are based upon the galactose concentration of the blood, it is very important to establish the galactose dosage according to body weight, because of the variation in the amount of intestinal absorptive surface, the blood volume, and the mass of liver and muscle tissue in subjects of different size. The normal subjects studied were medical students or laboratory workers with no evidences of abnormal conditions. Five male and five female subjects are included in the normal group. The diabetic subjects were patients in an out-patient diabetic clinic. These patients have received treatment for diabetes in this clinic from 1 to 7 years. They include two male and eight female subjects. Seven of the diabetic subjects were also given glucose tolerance tests with the same dosage of glucose as was used for the galactose tests. The glucose tolerance tests were given under conditions

similar to those of the galactose tests and within 1 to 2 weeks following the galactose tests. The galactose used was a c.p. grade of d-galactose with a specific rotation of $+$ 80.5°.

Results

The results of our experiments with normal subjects are shown in Table I. The maximum elevation of the blood galactose occurred in the sample collected 1 hour after ingestion in all cases but one, the latter showing a maximum elevation in the 2 hour sample. The highest elevation of blood galactose in the ten sub-

TABLE I

Galactose Tolerance of Normal Subjects

Subject	Galactose ingested	Blood sugar, mg. per 100 cc.								Urine sugar
		Galactose				Total sugar				Galactose in 2 hr. sample
		Control (saccharoid)	½ hr.	1 hr.	2 hr.	Control	½ hr.	1 hr.	2 hr.	
	gm.									*gm.*
A.M., ♂	66	8	29	37	32	75	88	95	89	1.00
A.S., ♂	61	7	35	39	36	79	86	90	88	2.25
J.R., ♂	75	9	56	63	33	80	107	118	92	2.48
R.E., ♂	64	9	32	67	30	78	91	112	97	1.00
H.D., ♀	74	7	28	80	34	78	98	118	87	0.91
F.B., ♀	60	10	53	100	29	89	120	142	96	1.35
C.S., ♀	44	7	90	109	34	70	125	139	89	0.92
E.B., ♀	58	9	53	89	118	76	94	132	156	2.20
G.Y., ♀	59	11	80	120	106	80	131	166	151	2.78
G.R., ♂	70	10	67	138	101	73	114	148	138	1.75

jects was 138 mg. per 100 cc.; the lowest was 39 mg. per 100 cc. The total sugar curves parallel the galactose curves in all cases. The 2 hour urine samples all contained galactose, the amounts ranging from 0.91 to 2.78 gm.   These results are in general agreement with the work of Harding and van Nostrand (3) who reported studies of the blood and urine galactose concentrations of normal subjects following the ingestion of 50 gm. doses of galactose, except that these authors did not obtain significant elevations of the non-fermentable sugar of the blood in seven of their fourteen subjects; whereas, we obtained definite elevations of the blood

galactose in all of our subjects. There is no evidence in these results of a higher tolerance for galactose in women than in men, as was reported by Rowe (11).

Our results with diabetic subjects are shown in Table II. The first significant observation from these data is that the elevation of the blood galactose following galactose ingestion is no greater in the ten diabetic subjects than that obtained with ten normal subjects. This relation is shown by the curves of Fig. 1. These

TABLE II

Galactose Tolerance of Diabetic Subjects

Subject	Sugar ingested	Galactose ingestion										Glucose ingestion			
		Blood sugar, mg. per 100 cc.								Urine sugar, 2 hr. sample		Blood sugar, mg. per 100 cc.			
		Galactose				Total sugar as glucose				Galactose	Total sugar as glucose	Glucose			
		Control (saccharoid)	½ hr.	1 hr.	2 hr.	Control	½ hr.	1 hr.	2 hr.			Control	½ hr.	1 hr.	2 hr.
	gm.									gm.	gm.				
H.C., ♂	50	5	18	20	16	408	416	439	388				190	228	266	247
M.J., ♀	50	9	25	47	21	105	114	140	109	0.29	0.23	90	160	220	173
A.S., ♀	60	11	22	77	31	186	242	296	257	0.58	0.46				
S.B., ♀	90	10		25	16	253	250	257	258	1.05	3.19	247	312	402	415
S.T., ♀	62	4	31	59	29	220	276	305	300						
E.L., ♀	60	8	32	52	24	218	280	294	256	1.15	2.14	224	272	356	426
H.Ck., ♀	72	5	18	34	41	179	189	235	247	0.72	1.15	151	240	275	302
M.P., ♀	60	7	51	99	35	205	272	348	305	3.94	8.73	226	330	384	424
H.S., ♂	62	8	52	73	22	410	500	547	500	1.65	10.88				
J.R., ♀	60	8	34	51	25	190	240	270	247	1.39	2.22	188	228	315	346

findings indicate that diabetics have as good a tolerance for galactose as normal subjects, a conclusion that is quite in contrast with the existing impression in the literature. A second significant observation from the data of Table II is that there is no greater excretion of galactose in the urine by the diabetic subjects than by the normal subjects. A third fact of importance is that the total sugar values of the blood parallel the galactose findings, but in some cases there is a greater increase in total sugar than in galactose. This relation is shown in Fig. 2. The curves showing
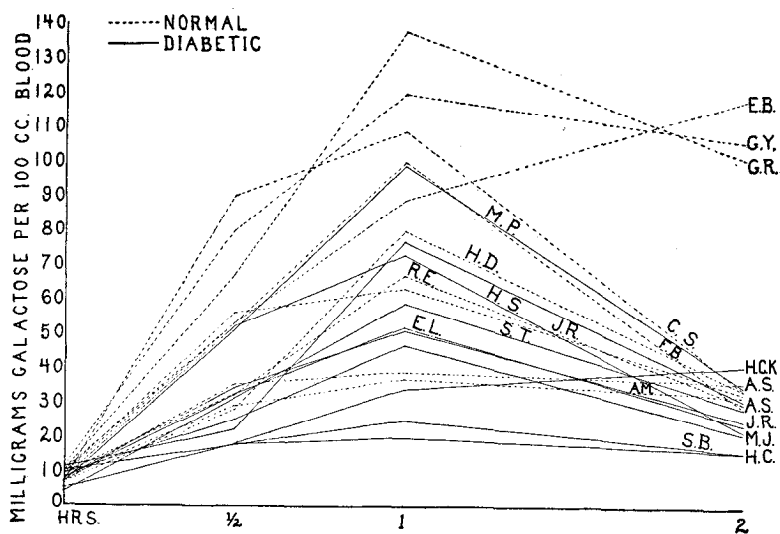
FIG. 1. Blood galactose curves following the ingestion of 1 gm. of galactose per kilo of body weight for ten normal and ten diabetic subjects.
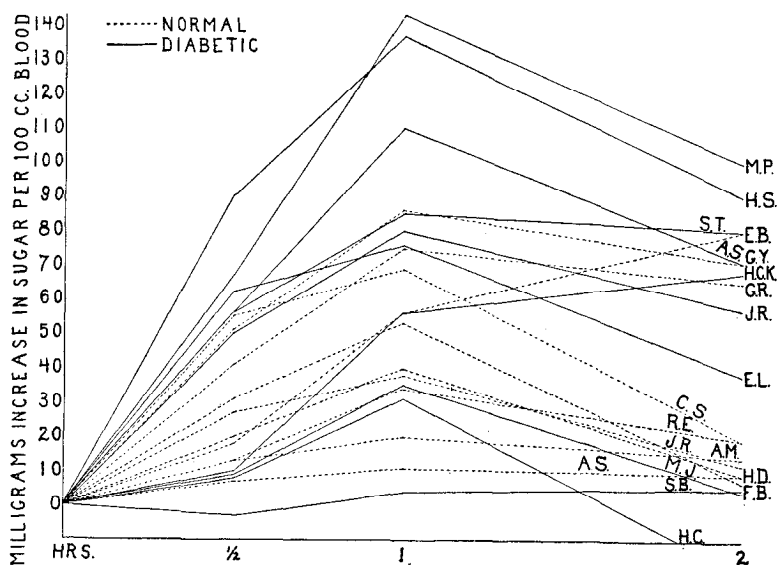

FIG. 2. Curves showing elevation of total blood sugar following the ingestion of 1 gm. of galactose per kilo of body weight for ten normal and ten diabetic subjects.

the elevation of the total blood sugar for seven of the diabetic subjects are well within the limits of the elevation of the total sugar curves of the normal subjects, but the curves for three diabetic subjects show a greater elevation than those of the normals. The greater increase in total blood sugar than in blood galactose following galactose ingestion is apparently due to conversion of galactose into fermentable sugar. This does not alter appreciably the demonstration that diabetics have good tolerance for galactose, because the elevations of total blood sugar were not marked in the three subjects showing greater increases in total sugar than was obtained with normal subjects. The evidence for conversion of galactose to fermentable sugar will be discussed later in this paper.

The observation that diabetics metabolize galactose practically as satisfactorily as normal subjects suggested to us the desirability of demonstrating the presence and the severity of the diabetes in these subjects by means of glucose tolerance tests, and of obtaining a comparison of the tolerance of diabetics for these two sugars. Accordingly glucose tolerance tests were given to seven of the diabetic subjects within 1 to 2 weeks following the galactose tolerance test, the condition of these subjects being unchanged at the time of the glucose test in so far as revealed by clinical observation and the blood sugar concentration. The amount of glucose administered was the same as the amount of galactose given in the galactose tolerance tests. The results of the glucose tolerance tests are shown in Table II. A characteristic diabetic elevation of the blood sugar was obtained in all subjects. The relation between the responses from galactose ingestion and glucose ingestion is shown in Fig. 3. In preparing these curves it was necessary to add a plus correction to the total sugar values obtained by galactose ingestion because the total sugar of the blood following galactose ingestion is a mixture consisting of both glucose and galactose. In determining these mixed sugars by Benedict's method, in which a glucose standard is used, the glucose is estimated correctly, but the galactose is underestimated because it has only 77 per cent of the reducing power of glucose. To correct for this underestimation of galactose it is necessary to add to the total sugar 23 per cent of the galactose value obtained in the separate estimation of the blood galactose. A correction calcu-

lated in this manner was added to the total sugar values obtained after galactose ingestion and these values were used for plotting the curves representing galactose tolerance in Fig. 3.   To simplify the comparison the galactose tolerance and glucose tolerance curves are started at the same origin.   The comparison shown by these curves is a striking one.   There is a marked spread between the two curves, and in all cases but one, the glucose tolerance
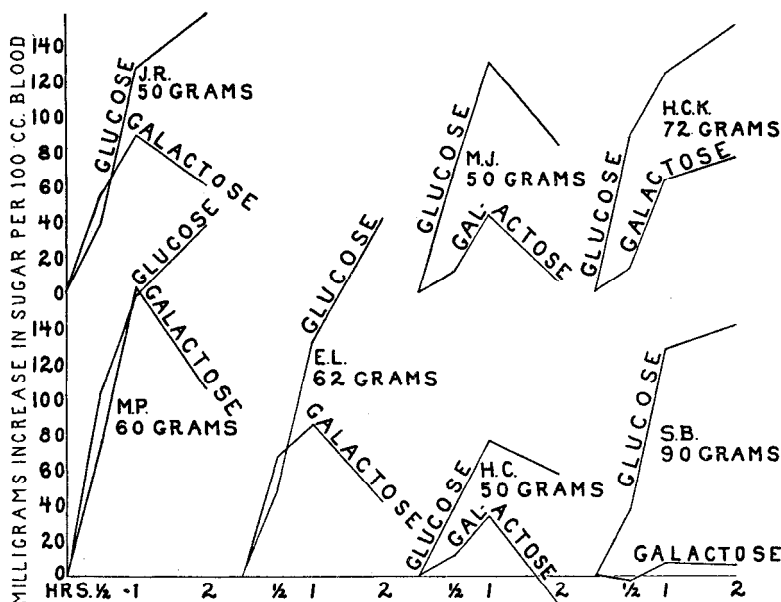
FIG. 3. Comparison of galactose and glucose tolerance of seven diabetic subjects, the dosage of galactose and glucose being the same in each case. The upper of each pair of curves shows the response following ingestion of glucose; the lower shows the results following the ingestion of galactose.

curves show maximum elevations at the end of the 2 hour period, while the galactose tolerance curves show a marked lowering at the end of the 2 hour period in all but one instance.   These findings demonstrate clearly the greater tolerance of diabetics for galactose than for glucose.

In seeking an explanation of the practically normal tolerance of diabetics for galactose a negative relationship of insulin to galactose metabolism seemed probable.   This conception is con-

trary to the existing opinion and evidence in the literature regarding the activity of insulin with respect to galactose. Corley (1) reported that insulin brought about a marked lowering of galactose in the blood of a rabbit when 1 gm. of galactose and 2 units of insulin in 15 cc. of water were injected intravenously. The uncontrolled experiment reported by Corley does not justify the conclusion he made. Just because the galactose content of the blood of a rabbit was lowered following insulin administration is no reason to assume that insulin is responsible for this lowering.

To examine the relation of insulin to galactose metabolism certain animal experiments were carried out. In our first experiments upon this problem mixtures of equal parts of galactose and glucose were given intravenously, or subcutaneously, and insulin, in doses calculated to be a little less than lethal for the amount of glucose administered, was injected subcutaneously. Samples of blood were then collected at intervals following administration of the sugars and the total blood sugar and blood galactose were determined upon these samples. In such experiments the total sugar curves may be interpreted as showing the effect of insulin upon glucose, since a considerable part of the total sugar under these conditions is glucose; and the galactose curves should represent the influence of insulin upon galactose in the blood. The value of such experiments is that they show the simultaneous effects of insulin in the same animal upon comparable amounts of circulating glucose and galactose. Typical results of such experiments upon rabbits and upon chickens are shown in Fig. 4. The slopes of the curves in Fig. 4 show a more rapid lowering of the total blood sugar than of the blood galactose. This effect continues until nearly all of the glucose has disappeared from the blood, at which time the total sugar curve and the galactose curve either cross or parallel each other. These experiments demonstrate that the effect of insulin upon glucose is certainly more marked than its influence, if any, upon galactose.

Further experiments upon this problem consisted of studying the rate of removal of injected galactose from the blood of rabbits with and without insulin administration. Two rabbits were given 2 gm. of galactose per kilo of body weight intraperitoneally, and, after waiting about 1 hour to permit the blood galactose to reach a peak level, samples of blood were collected at approxi-

mately ½ hour intervals until 3 hours after injection of the sugar. In this way control values upon the rate of removal of galactose
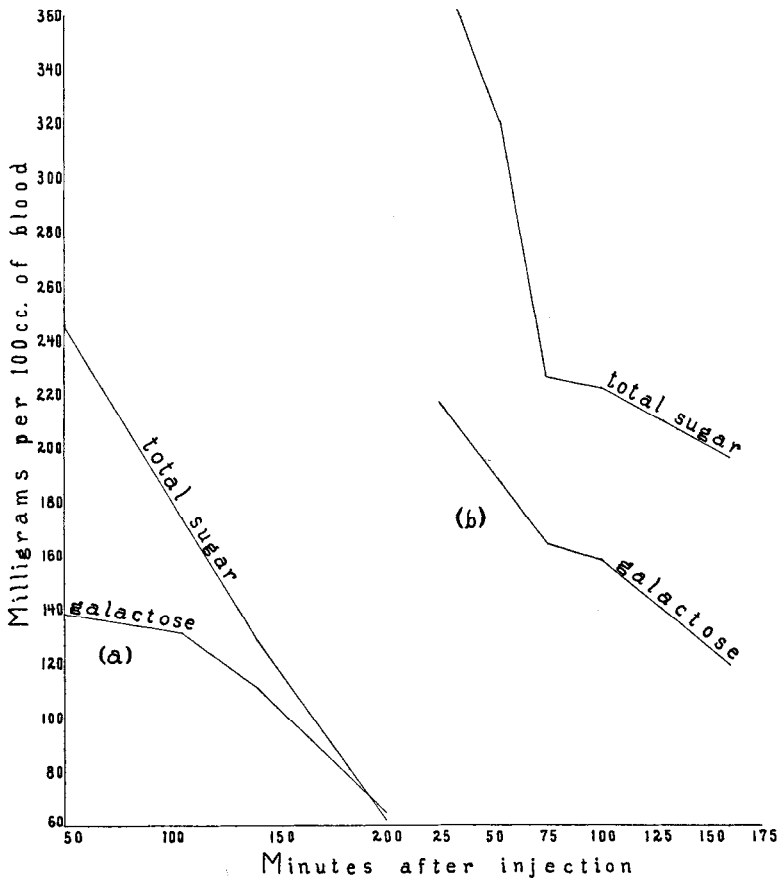
FIG. 4. Total blood sugar and blood galactose curves following the administration of 2 gm. of glucose, 2 gm. of galactose, and 4 units of insulin per kilo of body weight to a rabbit (a) and 2 gm. of glucose, 2 gm. of galactose, and 2 units of insulin per kilo of body weight to a chicken (b).   The sugar was given to the rabbit subcutaneously and to the chicken intravenously.

from the blood were obtained.   Upon the following day this experimental procedure was repeated with the additional step of injecting 9 clinical units of insulin following the galactose adminis-

tration.   Care was taken to inject the same dosage of galactose
in the same manner and blood samples were collected at intervals
corresponding to those of the control procedure.   The results of
these experiments are shown in Fig. 5.   The curves obtained with
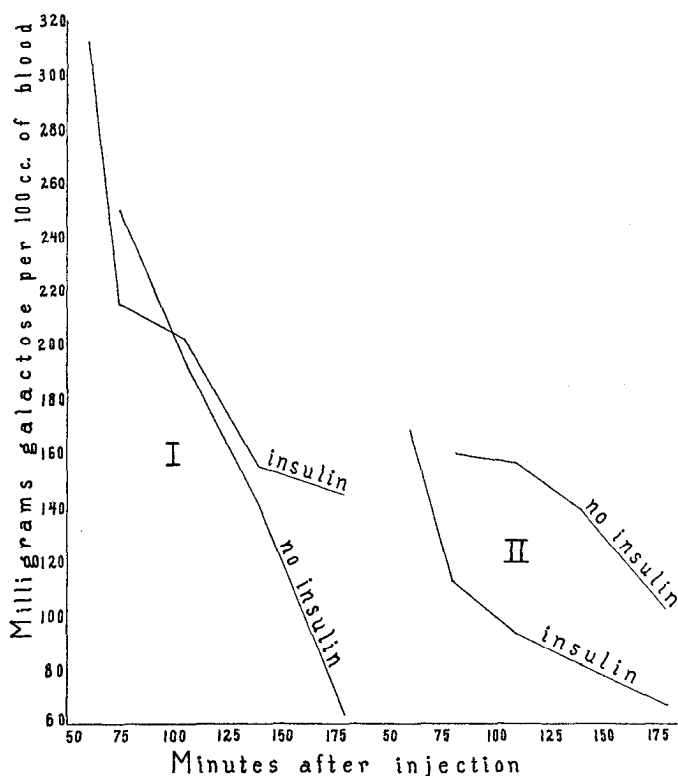insulin administration show a little less drop in the blood galactose

FIG. 5. Blood galactose curves obtained upon rabbits given 2 gm. of gal-
actose per kilo of body weight with and without insulin administration.

than was obtained over the corresponding period in the control pro-
cedure in which insulin was not injected.   To make sure that the
insulin was potent the rabbits were observed until insulin con-
vulsions occurred, and blood samples were collected at the stage
of convulsions and analyzed for fermentable sugar, the results
of these analyses showing that a hypoglycemia existed.   The

failure of toxic doses of insulin to influence the removal of galactose
from the blood of rabbits, as shown by these experiments, is con-
vincing evidence that insulin does not affect the anabolism of
galactose.

To study further the relation of insulin to galactose metabolism
it was decided to investigate the ability of galactose to detoxify
lethal doses of insulin. The experiments carried out by us con-
sisted of giving large doses of galactose subcutaneously to rabbits,
followed by injection of about 3 times the lethal dose of insulin.
The results of these experiments are shown in Table III. In
three experiments 10 gm. of galactose failed to prevent the onset
of insulin convulsions when 10 clinical units of insulin were in-
jected, and in one experiment 20 gm. of galactose did not prevent
convulsions, the insulin dosage being 15 clinical units. A sample

TABLE III

Showing Galactose Is Not a Physiological Antagonist to Insulin

Rabbit No.	Clinical units of insulin injected	Galactose injected	Blood galactose at time of convulsions
		gm.	*mg. per 100 cc.*
I	10	10	150
II	10	10	254
III	10	10	270
IV	15	20	409

of blood was collected from the marginal ear vein of the rabbits
after convulsions had occurred and the animal was in collapse,
and these samples were analyzed for galactose by our method and
for total sugar by Benedict's method. The total sugar values
were the same within the limits of experimental error before and
after yeast fermentation, showing that the glucose had practically
all disappeared. The analyses for galactose showed values rang-
ing from 150 to 409 mg. of galactose per 100 cc. of blood. The
onset of insulin convulsions following insulin and galactose ad-
ministration, and the demonstration of large amounts of galactose
in blood collected during the stage of insulin convulsions, are
indisputable proof that galactose is not a direct physiological
antagonist to insulin. This finding is also further evidence that
insulin does not influence the anabolism of galactose.

The power of galactose to detoxify insulin has been studied by other workers. Noble and Macleod (12) have reported that galactose injected subcutaneously has a slight antidote effect upon insulin but does not prevent insulin convulsions in rabbits given toxic doses of this hormone. Voegtlin, Dunn, and Thompson (13) found that galactose has almost as good a protective influence against minimum lethal doses of insulin administered to rats as has glucose, when the sugar is given by way of the alimentary tract with a stomach tube. Our work on the other hand has shown that galactose is not a physiological antagonist to insulin. These reports may be harmonized by assuming that following galactose administration there is some conversion of galactose into a sugar that has an antidote effect upon insulin. The conversion of galactose into a sugar that is a specific antidote for insulin would account for the slight detoxifying effects obtained by Noble and Macleod by subcutaneous injection of galactose, and would explain the more marked detoxifying effects obtained by Voegtlin, Dunn, and Thompson as there is probably more conversion when the sugar is administered by way of the alimentary tract. Such a hypothesis is in harmony with our finding that galactose *per se* is not an antidote for insulin. Later in this paper we will discuss other evidence for the conversion of galactose into fermentable sugar following galactose ingestion.

In the experiments described above it has been shown that (1) insulin injected into animals following the administration of equal quantities of glucose and galactose has a marked effect upon the lowering of the blood glucose and that its influence, if any, upon the blood galactose is uncertain; that (2) toxic doses of insulin, when administered to rabbits which have received galactose intraperitoneally, did not cause a more marked lowering of the blood galactose than was obtained in control experiments in which the rabbits were given the same dosage of galactose but did not receive insulin; that (3) galactose is not a physiological antagonist to insulin. These findings are convincing evidence that insulin does not influence the anabolism of galactose, a conclusion which is in harmony with our observation that the removal of galactose from the blood is as rapid in diabetic subjects as in normal subjects.

Is Galactose Converted to Fermentable Sugar during or following Absorption?

The data of our experiments with human subjects have a bearing upon the question of whether galactose is converted to fermentable sugar during or following absorption from the alimentary tract. If the increase in total blood sugar following ingestion of galactose is greater than the increase in blood galactose, there is either conversion of galactose into fermentable sugar, or else a physiological stimulus bringing about increased glycogenolysis has occurred. Our experiments yielded data which are capable of analysis for increases in blood galactose and total blood sugar.   To get the increase in blood galactose we subtract the saccharoid value of a control sample of blood obtained before galactose ingestion from the galactose values of samples of blood collected after galactose ingestion.   To calculate the increase in total blood sugar we first correct the total sugar values by adding 23 per cent of the galactose found in the same sample of blood by the separate analysis for galactose; this correction is valid, because the galactose fraction of the total blood sugar was underestimated 23 per cent by being determined against a glucose standard.   From the corrected total blood sugar values we then subtract the initial total sugar value obtained upon a control sample of blood collected before ingestion of galactose; this gives the increase in total blood sugar following galactose ingestion.   The analysis of our data is given in Table IV. In this table is shown the difference between the total blood sugar increase and the blood galactose increase, expressed as increase in fermentable sugar, in the $\frac{1}{2}$ hour, 1 hour, and 2 hour samples of blood collected following galactose ingestion in both the normal and diabetic subjects.   A definite contrast in findings occurs.   In the normal subjects slightly negative values for fermentable sugar are obtained in nearly all cases; in the diabetic subjects positive values for fermentable sugar that represent increases beyond the limits of experimental error are the rule.   The positive values for increases in fermentable sugar obtained upon diabetic subjects must be interpreted as indicating that either there was a conversion of galactose into fermentable sugar or that increased glycogenolysis occurred.   That increased glycogenolysis occurred in the diabetic subjects following galactose ingestion seems very

improbable because the increase in the monosaccharide content of the blood by absorption from the intestinal tract would certainly oppose the glycogenolysis reaction. It seems probable, therefore, from our experiments, that in diabetic subjects there is a small amount of conversion of galactose into fermentable sugar following galactose ingestion, either during absorption from the intestinal tract or while the galactose is present in the blood. This conclusion is in harmony with the fact that diabetic subjects store glucose poorly, and hence, if conversion of galactose occurs,

TABLE IV

Difference between Total Sugar Increase and Galactose Increase in Blood Following Galactose Ingestion

Calculated from the data of Tables I and II.

Normal subjects				Diabetic subjects			
	Fermentable sugar per 100 cc.				Fermentable sugar per 100 cc.		
Subject	½ hr. sample	1 hr. sample	2 hr. sample	Subject	½ hr. sample	1 hr. sample	2 hr. sample
	mg.	*mg.*	*mg.*		*mg.*	*mg.*	*mg.*
A.M.	−3	−2	−5	H.C.	−2	+19	
A.S.	−15	−14	−14	M.J.	−4	+6	−6
J.R.	−9	−5	−6	A.S.	+47	+59	+56
R.E.	−5	−11	+3	S.B.		−8	0
H.D.	+4	−16	−12	S.T.	+35	+43	+61
F.B.	−3	−16	−8	E.L.	+43	+42	+25
C.S.	−9	−10	−2	H.Ck.	0	+34	+40
E.B.	−16	−6	−4	M.P.	+32	+72	+78
G.Y.	−2	+2	−2	H.S.	+56	+87	+79
G.R.	+5	−24	−5	J.R.	+30	+47	+44

fermentable sugar will tend to accumulate in the blood. Our data upon normal subjects do not give evidence either for, or against, conversion of galactose into fermentable sugar following galactose ingestion, yet some conversion may have occurred, because normal subjects store glucose rapidly and possibly with increases in blood galactose the mechanism is to lower the blood sugar by storage of glucose. Such a mechanism would account for the negative values for increases in fermentable sugar in the blood of our normal subjects following galactose ingestion.

Utilization of Galactose

Harding and van Nostrand (3) have studied the utilization of galactose and have corrected the impression in the literature that galactose is a poorly utilized sugar. The idea that galactose is poorly utilized arose from qualitative studies of the urine following galactose administration. By means of quantitative studies of urinary galactose excretion Harding and van Nostrand showed that galactose is well utilized by the human body. These authors gave 50 gm. of galactose by mouth and found a utilization of 97 per cent in half of their subjects, as measured by urinary galactose excretion. The poorest utilization observed by Harding and van Nostrand was 86 per cent of ingested galactose. We cannot draw conclusions regarding complete utilization of galactose from our data, because in our experiments only 2 hour quantities of urine were collected, and galactose is excreted in the urine for a longer time than 2 hours after ingestion of such doses as we used. Our studies of urinary galactose excretion were carried out to obtain a comparison of the utilization of galactose by normal and diabetic subjects. Our results show no greater excretion of galactose in the urine by the diabetic subjects than by the normal subjects. Two of our diabetic subjects, M. J. and A. S., showed a low galactose excretion and no glucose excretion. In the other diabetic subjects there was both glucose and galactose excretion in the urine. The glucose excretion in these cases was no greater than would seem to be warranted by the degree of hyperglycemia that existed. The results of our comparative urinary sugar excretion studies indicate that the utilization of galactose by diabetics is as good as its utilization by normal subjects.

Clinical Import

From our experiments certain clinical possibilities are suggested. Our data show that galactose is well tolerated by diabetics when given in large doses. The administration of galactose in smaller amounts along with other foods should result in even better tolerance and less urinary excretion. It, therefore, seems probable that galactose might be made a valuable adjunct to the diet in the clinical management of diabetes mellitus. The use of a

sugar that has nutritive value and a satisfying sweetness, and whose administration by mouth produces practically no greater saccharemia in diabetics than in normal subjects, should mark considerable advance in the control of diabetes mellitus and its undesirable consequences, such as diabetic retinitis and endarteritis, conditions which are presumably etiologically related to hyperglycemia. Our work has demonstrated that galactose ingestion by the diabetic does not produce the hypersaccharemia characteristic of glucose ingestion, and that this is apparently because insulin is not necessary for the anabolism of galactose. Deuel, Gulick, and Butts (14) have reported that galactose has a higher antiketogenic value than glucose, an observation that suggests further possibilities from galactose feeding to diabetic patients. However, a complete evaluation of the possibilities of galactose feeding in diabetes mellitus is conditioned upon further knowledge of the metabolism of galactose, and of the part played by insulin in carbohydrate catabolism.

SUMMARY

1. A method for the determination of galactose in blood is described.

2. The galactose tolerance of ten normal and ten diabetic subjects has been studied by the determination of the blood galactose, total blood sugar, and urinary galactose, following the ingestion of 1 gm. of galactose per kilo of body weight.

3. The blood galactose values following galactose ingestion obtained with diabetic subjects were in all cases within the limits of the values obtained with normal subjects upon the same galactose dosage.

4. The total blood sugar increases following galactose ingestion were no greater in seven of the diabetic subjects than the total blood sugar increases obtained with normal subjects. The other three diabetic subjects showed slightly greater total blood sugar increases following galactose ingestion than was obtained with normal subjects, a result which is apparently due to the conversion of galactose to fermentable sugar.

5. It has been shown that toxic doses of insulin do not change the rate of removal of galactose from the blood of rabbits and that galactose is not a direct physiological antagonist to insulin. It

seems evident, therefore, that insulin does not influence the anabolism of galactose. This conclusion offers a satisfactory explanation of our data showing that diabetics have practically as good a tolerance for galactose as normal subjects.

6. Clinical possibilities of the use of galactose in the control of diabetes mellitus are suggested.

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ARTICLE:

GALACTOSE TOLERANCE OF NORMAL AND DIABETIC SUBJECTS, AND THE EFFECT OF INSULIN UPON GALACTOSE METABOLISM

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