THE UTILIZATION OF INTRAVENOUSLY ADMINISTERED GLUCOSE, FRUCTOSE, AND INVERT SUGAR IN CATTLE

by

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INTRODUCTION

The demonstration that insulin affected phosphorylation of glucose and that specific hexokinases for fructose and glucose existed in the liver led to investigations with fructose as a therapeutic agent in diabetes mellitus and other disturbances of carbohydrate metabolism. Later studies indicated separate metabolic pathways for glucose and fructose and that fructose metabolism was not affected in diabetes. Further investigations showed that the utilization of fructose was not dependent on insulin in normal dogs and that fructose was more easily phosphorylated than glucose. Other workers have demonstrated less urinary loss from intravenously administered fructose and invert sugar as compared with glucose. Direct assimilation of fructose by peripheral tissues has likewise been demonstrated. When normal dogs were compared with dogs made acidotic with ammonium chloride it was found that the rate of disappearance of glucose from the blood was slower in the acidotic animal than in the normal individual, indicating that acidosis inhibited cellular uptake of glucose and/or processes of phosphorylation. Recent work has shown fructose to be ketolytic in depancreatized ketotic dogs. These findings suggested a need for an evaluation of the utilization of fructose and invert sugar in cattle since it is well known that ruminants differ markedly in their carbohydrate metabolism from that of monogastric animals. Further, in case of greater advantages of these sugars over glucose, their superiority as valuable therapeutic agents would be indicated in the

many disturbances of the ruminant where therapy with glucose is employed and especially in ketosis of dairy cattle.

REVIEW OF LITERATURE

Fructose and Invert Sugar

The use of fructose in carbohydrate therapy was first suggested by Minkowski (47) in 1893. This worker, using dogs made diabetic by extirpation of the pancreas, showed that fructose was better tolerated in these experimental animals than glucose. Cori (12), studying the rate of glycogen formation in the liver of normal and insulinized rats during the absorption of glucose, fructose, and galactose, found that glucose and fructose are on a par as glycogen formers even though glucose was absorbed twice as fast as fructose. It was further shown that large doses of insulin almost completely suppressed the glycogen formation in the liver from glucose and from fructose. Wierzuchowski (78), using normal dogs, found higher blood sugar values following intravenous infusion of glucose when compared to fructose infusion. Employing these same experimental animals it was shown further that insulin had no effect on fructose utilization whereas glucose excretion dropped from 10 per cent to 1 per cent following insulin injection. Similar findings in rats were reported by Cori and Cori (13). These workers, however, found fructose less readily retained by the kidneys when compared to glucose. They likewise reported that insulin had no effect on fructose

utilization whereas large doses of insulin raised the intravenous glucose tolerance about 20 per cent. Davidson et al. (15), injecting fructose intravenously into rabbits previously infused with glucose, found a more rapid fall in blood glucose as compared to glucose injection. They concluded that fructose stimulated the production of insulin. Insulin, on the other hand, had no effect on the rate of disappearance of blood fructose. Using rat liver slices and homogenates in the presence of adenosine triphosphate (ATP), $MgCl_2$, ketoglutarate, and a phosphate buffer, Vestling et al. (74) demonstrated that fructose phosphorylation occurred ten times more readily than glucose phosphorylation in vitro. Weinstein (76, 77) showed that when an invert sugar solution containing equal quantities of glucose and fructose was injected into human subjects less glycosuria was produced than when glucose was employed alone.

The comparative utilization of fructose and glucose given intravenously has been investigated by Weichselbaum et al. (75). In ten experiments on normal human subjects comparative intravenous injections of 10 per cent glucose and 10 per cent fructose were carried out. Even at rapid rates of infusion very little fructose appeared in the urine as compared to the amount of glucose. Diuresis was also less pronounced with fructose. Moreover, the fructose infusions were not followed by either hyperglycemia nor by an excessive rise in the blood fructose level, thus indicating a more rapid utilization of fructose and presumably more rapid glycogenesis. Conversely, this investigator demonstrated that continuous intravenous alimentation with glucose

stimulated the pancreas to produce increased amounts of insulin and thus led to hypoglycemia following intravenous injection.

Brady and Gurin (5) showed that liver slices from normal rats and cats readily converted C^{14} labeled acetate to long chain fatty acids. However, liver slices of alloxanized rats and pancreatectomized cats are relatively incapable of carrying out this process. The addition of insulin, glucose, fructose-6-phosphate, oxalacetate, or ketoglutarate to the incubating medium failed to re-establish fatty acid synthesis in liver slices from these animals. Similar experiments using alloxan diabetic rats have shown a reduction in the capacity of liver slices from these animals to convert glucose, fructose, acetate, lactate, and pyruvate to fatty acids (8, 10, 11, 23, 52). However, other investigators (9) using similar experimental animals and conditions demonstrated a restoration of the ability of the previously insulin treated liver slices to convert C^{14} glucose to fatty acids as well as oxidize it to carbon dioxide. The ability of insulin treated, alloxan diabetic livers to convert C^{14} labeled acetate and formate to fatty acids has likewise been demonstrated (23). Chernick and Chaikoff (8), once more using C^{14} labeled glucose, fructose, and acetate and employing liver slices from normal and alloxan diabetic rats, found the conversion of glucose to both carbon dioxide and fatty acids to be markedly depressed in the diabetic liver. On the other hand, the oxidation of fructose and acetate to carbon dioxide proceeded at normal rates in the diabetic liver although its conversion to fatty acids was impaired. Thus defective lipogenesis in the diabetic

liver can be repaired in two ways, viz., by insulin injections or by fructose feeding. However, the actions of the two treatments upon lipogenesis are not identical. The hormone repairs lipogenesis not only from acetate, lactate, and pyruvate, but also from glucose (9). Fructose feeding, on the other hand, repairs lipogenesis from the two-carbon intermediate but not from glucose (1). This difference indicated that the feeding of fructose by circumventing the initial block in glucose utilization provided a continuous source of substrates in the glycolytic system. This demonstrated that an active glycolytic system is required for maintenance of lipogenesis in the liver. Support for such a view is found in the rapid decrease in lipogenesis from glucose and acetate that occurs in the fasted rat and in the rat fed a diet totally devoid of carbohydrate (5).

Wyshak and Chaikoff (82) compared the relative abilities of liver slices from normal and fasted rats to metabolize radioactive glucose and fructose since glucose utilization is temporarily inhibited following a prolonged fast (7). It was learned that the abilities of livers from rats fasted 72 hours to convert glucose to carbon dioxide decreased by about 50 per cent; however, livers from rats fasted under similar conditions showed no significant difference in their abilities to oxidize fructose.

Early studies on the renal threshold of fructose in man found it less readily retained by the kidneys when compared to glucose (81). Other investigators (46, 67) found that similar amounts of glucose and fructose (less than 10 per cent) appeared in the urine following the infusion of these two sugars in normal

human subjects. Weinstein (76, 77), using normal human beings, reported that invert sugar solutions are retained more readily in the body than either fructose or glucose. Frost et al. (24), comparing the tolerance of rapidly injected glucose and invert sugar in normal ambulatory young men, demonstrated less urinary loss of reducing substances following invert sugar infusions. Rice and Strickland (56) reported that invert sugar produced less hyperglycemia and less glycosuria in surgical patients than when glucose was used as the source of carbohydrates. However, Smith et al. (68) failed to disclose any advantage of invert sugar over glucose with regard to renal tolerance. Moncrief et al. (48) in one series of observations in humans compared fructose and glucose on alternate days in the same patient after surgical operation. Under these conditions, total 24 hour urine specimens showed an average loss of 25.3 gm of reducing sugars on the days when glucose was infused as compared with a loss of 9.9 gm when fructose was administered.

Five diabetic and three normal human subjects were used by Miller et al. (46) to compare the utilization of fructose and glucose. In normal subjects fructose produced a much greater rise in blood pyruvic acid and a rise rather than a fall in plasma citrate as compared to glucose. Fructose also disappeared more rapidly from the blood stream. In diabetic subjects, in the absence of insulin, fructose produced the same rise in pyruvic acid as was found in normal subjects, while glucose produced either a slight or delayed rise. Increases in plasma citric acid after fructose administration were similar to those in

normal individuals. The blood fructose disappearance curve and the amount of fructose excreted in the urine in patients with diabetes were the same as in normal subjects. Fructose invariably produced a fall in serum inorganic phosphate, while a fall did not usually occur after glucose. These studies indicated that the metabolism of fructose differs from that of glucose in both the normal and diabetic subject and that the metabolism of fructose in the diabetic individual is similar to that in the normal even in the absence of insulin.

In further detailed studies on the administration of fructose solutions to patients with diabetes, Smith et al. (67) found the impairment of fructose tolerance in such patients was relatively small and not at all comparable to impairment in tolerance of the same patients to glucose. When amounts of serum inorganic phosphate following glucose and fructose administration were compared, it was noted that the phosphate levels fell more rapidly after fructose administration and also returned more rapidly to normal. Much higher levels of such carbohydrate intermediates as pyruvate, lactate, and alpha-ketoglutarate were found in the blood following fructose injection. These observations are consistent with the theory that the phosphorylation of glucose to glucose-6-phosphate is impaired in diabetes, while the phosphorylation of fructose, which is uninfluenced by insulin, proceeds at a normal rate.

Van Itallie et al. (73), in further studies on fructose utilization, measured the peripheral fructose differences in arterial and venous blood. In this study ten human subjects

receiving a constant intravenous infusion of ten per cent fructose, following an initial priming injection, were employed. Maintenance of consistent and appreciable arteriovenous differences under these circumstances occurred in every case thus indicating direct assimilation of fructose by peripheral tissues.

Mackler et al., using dogs made acidotic by hepatectomy (41) or by the injection of ammonium chloride (40), found the disappearance of glucose from the blood was slower in acidotic than in non-acidotic states. This investigation indicated that acidosis inhibits the cellular uptake of sugar by interfering with the production of insulin and/or with the action of insulin in bringing about processes of phosphorylation.

The comparative effects of intravenously administered glucose, glucose plus insulin, and fructose on the concentrations of ketone bodies in the blood and their excretion in the urine of dogs were studied by Whittlesey and Zubrod (79). The experimental animals were totally depancreatized and deprived of exogenous insulin for periods of four to ten days. The effect observed following fructose administration was similar to that seen with the infusion of glucose plus exogenous insulin, viz., a fall in the blood concentration of ketone bodies. This fall was not the result of urinary excretion of ketone bodies. Glucose infusion alone was accompanied by a continued rise in ketone body concentration in the blood. This indicated that fructose in the absence of insulin is ketolytic when administered to depancreatized, ketotic dogs.

Metabolic Pathways of Carbohydrates, Fats, and Proteins

During recent years significant advances have been made in the understanding of intermediary metabolism. With this advancement has come an increase in the knowledge of the various pathways by which the major metabolites--carbohydrates, fats, and proteins--are utilized by the animal body. Recent reviews on fat metabolism by Lehninger (36) and Lipmann (38) have indicated the central role of coenzyme A (CoA) in the intermediary metabolism of these metabolites (Fig. 1).

Carbohydrate Metabolism. The anaerobic pathway of glucose metabolism has been known for some time. Upon absorption, glucose may be stored as glycogen or if needed for energy may be phosphorylated and broken down to pyruvate. Pyruvic acid may be further oxidatively decarboxylated to form carbon dioxide and acetate or it may be carboxylated to form oxalacetate (39, 50, 51). If decarboxylation occurs, the acetate then may combine with CoA to form acetyl CoA and thus enter the tricarboxylic acid energy cycle.

Fat Metabolism. In the utilization of fats, it is first necessary that they be hydrolyzed to fatty acids and glycerol. In order for fatty acid oxidation to proceed it is necessary that the oxidation of tricarboxylic acid cycle intermediates be proceeding normally so that a continuous supply of ATP may be available as a source of high energy bonds (14). Lehninger (36), Lipmann (38), and Green (25) have described the process of fatty acid oxidation as being one in which the fatty acid molecule

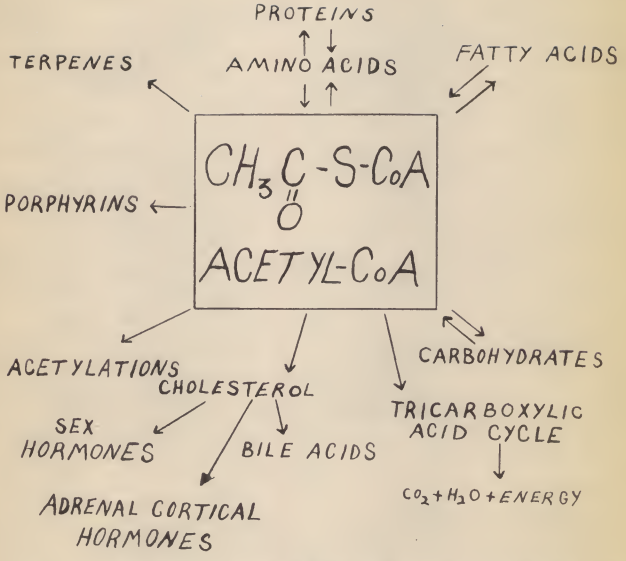

FIG. 1. The central place of acetyl-CoA in intermediary metabolism.

forms a complex with CoA. The CoA-fatty acid complex then undergoes beta oxidation in which a two-carbon unit is split off and which combines with another CoA molecule to form acetyl CoA. The acyl CoA residue again undergoes successive beta oxidation until the acid has been degraded to an acetoacetyl CoA fragment. This last C_4 fragment may be degraded further to acetyl CoA or it may be hydrolyzed to free acetoacetic acid (4). Acetoacetic acid may be metabolized after once more combining with CoA or it may be decarboxylated to acetone. Normally the latter pathway appears to be followed only to a minor degree (4). The glycerol portion of the fat molecule is oxidized to triose phosphate and may then form pyruvic acid (17, 18). Acetic, propionic, and butyric acids (4, 25) must first be activated to form a complex with CoA before their utilization is possible.

Protein Metabolism. Prior to utilization, proteins are hydrolyzed to their constituent amino acids. The amino acids may then be converted to keto acids by direct deamination or by transamination (69). The keto acids thus formed may combine with CoA and thus, as in the case of carbohydrates and fats, enter the tricarboxylic acid cycle. Several of the keto acids formed during the deamination process may form glycogen (6, 26, 27).

Ruminant Nutrition and Ketosis

Several investigations by Schambye (58, 59) in which arterial and portal blood glucose differences were measured in sheep

have shown that carbohydrate metabolism in ruminants differs from that in monogastric animals. Results of these studies indicated that little glucose is absorbed from any part of the digestive system of the sheep. These findings have been substantiated by other workers (20, 32, 45, 54, 55). Thus, monosaccharides, as such, are not a significant source of energy to the ruminant.

Holmes (30), studying the effects of administering glucose by mouth to normal cattle of all ages, found that young calves acted as monogastric animals and showed a higher and more prolonged rise in blood sugar. He likewise found the appearance of acetone bodies in the urine of adults following glucose feeding but no acetonuria in the young animals under similar conditions. This suggests a relationship between rumen function and acetone production. This worker reported anorexia, rumen atony, and diarrhea when glucose was given per os to the ruminant animal.

Formerly it was recognized that cellulose is digested with the aid of bacteria in the rumen. It has now been conclusively demonstrated that, unlike other animals, the ruminant is largely dependent upon the products of microbial fermentation and upon the micro-organisms themselves for its metabolic needs (34). The energy needs are supplied largely by short chain organic acids formed during carbohydrate fermentation (20). It has been demonstrated that these acids are absorbed directly by the rumen wall (52, 54).

Numerous investigators have shown the relationship between the rumen and rumen fermentation and ketosis (21, 22, 28, 31-34,

60, 61). It has been known for some time that the ketotic ruminant has a low blood sugar level and that intravenously administered glucose in many instances will alleviate the condition. Johnson (34), in a theoretical discussion of ruminant ketosis, pointed out that one effect of the low blood sugar values is the use of oxalacetate for the synthesis of needed glucose. As oxalacetic acid is essential in the proper functioning of the tricarboxylic acid cycle, a shortage of this substance would have far reaching effects on the metabolism of the animal. Moreover, any further oxalacetate formed during the oxidation of butyric and propionic acids could conceivably be used up rapidly in the synthesis of needed glucose. In the absence of oxalacetate, acetic acid, normally one of the principal sources of energy to the ruminant, becomes of no value. Further, it may even become a liability if it is condensed to acetoacetic acid, one of the ketone substances found to be very prevalent in ketosis. Under these circumstances body fat is utilized in an attempt to overcome the shortage of energy. This process, under the conditions shown to be present in ketosis, would result in a further build-up of ketone substances formed during fatty acid oxidation.

In most animals, when exogenous carbohydrate is lacking, proteins are broken down to supply the demand. This process of gluconeogenesis has been shown to be of little importance in the ruminant animal by McCandless and Dye (42, 43, 44). The important role played by the rumen and rumen flora has been pointed out by Underbjerg (71). It was further discussed how a dysfunction of this key organ could induce a nutritional metabolic

stress and thus lead to tissue depletion of essential metabolites. Anorexia and rumen atony have been shown to be early symptoms of ketosis in cattle. Regardless of whether they are a cause or a result of ketosis, anorexia and rumen atony would certainly decrease exogenous sources of energy. Further tissue and fat breakdown would then be required to meet energy needs and thus result in a further increase in ketone substances.

Past treatments to alleviate the condition of ketosis have been discussed by Underbjerg et al. (72). It was pointed out that these treatments are all directed at supplying glucose and/or energy either directly or indirectly. Intravenous glucose constitutes a direct way of supplying energy to the ketotic animal. Shaw et al. (66) suggested that in the treatment of ketosis with glucose, this compound should be administered periodically. Cortisone and adrenocorticotropic hormone (ACTH) bring about gluconeogenesis whereby body protein is broken down in order to supply needed energy (63, 64). Obviously this is a biologically expensive way to supply energy to an animal whose energy metabolism is already functioning improperly. As pointed out by these and other workers sodium acetate (72), sodium propionate (60), glycerol (34, 35) and propylene glycol (35), given per os, can also be utilized for energy. After their absorption they follow the normal metabolic routes followed by short chain fatty acids.

MATERIALS AND METHODS

Twelve yearling Hereford heifers having an average weight

of 822 pounds were employed in this investigation. These animals were fed a balanced ration high in concentrates. The basal ration fed daily to calves 25, 29, 30, 32, 33 and 36 consisted of the following:

Cracked yellow corn	11.0 lbs
Linseed meal	2.5 lbs
Wheat straw	ad. lib.
Iodized NaCl	20 gms
Calcium carbonate	36.08 gms
Feeding oil, containing 9 mg carotene/gm	7.6 gms

The basal ration fed daily to calves 26, 27, 28, 31, 34 and 35 consisted of the following:

Cracked yellow corn	11.0 lbs
Linseed meal	2.0 lbs
Alfalfa hay	2.0 lbs
Wheat straw	ad. lib.
Iodized NaCl	20 gms
Calcium carbonate	11.84 gms
Feeding oil, containing 9 mg carotene/gm	3.6 gms

Each calf was injected intravenously with glucose, fructose, and invert sugar at two week intervals. The sugars were dissolved in water to make 50 per cent solutions and were given at the rate of 0.5 gm/kg body weight. The invert sugar was prepared by mixing equal quantities of glucose and fructose so that the resulting solution contained 25 per cent glucose and 25 per cent fructose. The jugular vein was used as the injection site. Approximately five minutes were required for the administration. Blood samples were obtained from the jugular vein prior to and following the injection. The post-injection blood samples were obtained at two minutes, 30 minutes, one, two, four, and six hours following the injection. A mixture which has been shown

to stop enzymatic activity and which contained sodium fluoride, thymol, and sodium oxalate was used as the anticoagulant (37). Urine samples were collected prior to and one, two, four, and six hours following the infusions. In addition, the total urine formed and voided during the six hour post-injection period was collected from five calves in each group. Urination was induced by perineal stimulation. The blood and urine samples were refrigerated immediately upon collection and protein-free filtrates were prepared within three hours. This was done to prevent the breakdown of any glucose or fructose present in the blood or urine at the time of collection. The blood glucose was determined according to the method of Nelson (49) while blood fructose was determined by the method described by Roe et al. (57).

Duplicate glucose and fructose determinations, using an M14 Coleman spectrophotometer, were made on each blood and urine sample. Standard calibration curves for the determination of glucose and fructose are shown in Figs. 2 and 3. These curves were established prior to and checked periodically throughout the experiment. The calibrations were accomplished by using standard solutions containing known amounts of glucose and fructose.

RESULTS AND DISCUSSION

Blood Analysis

The blood sugar values of the 12 calves before and following the intravenous infusions are shown in Table 1. The average

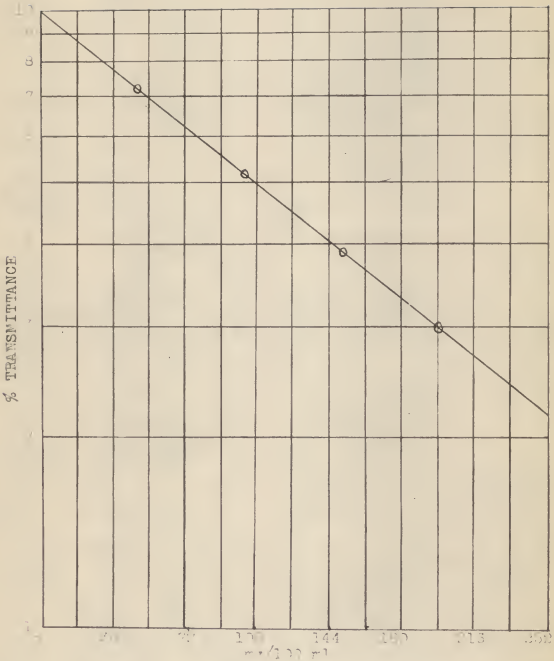

Fig. 2. Calibration curve used for the calculation of [illegible] in 1.0 ml.

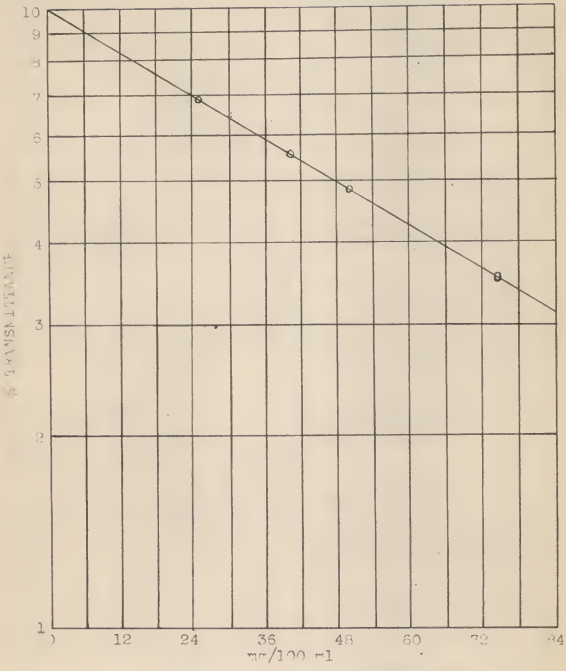

Fig. 3. Calibration curve used for the calculation of fructose values in mg/100 ml.

Table 1. Blood sugar determinations expressed in mg/100 ml following intravenous infusion of glucose at the rate of 0.5 gm/kg body weight.

Calf	Sample time						
Number	Pre-injection	2 Min.	30 Min.	1 Hr.	2 Hr.	4 Hr.	6 Hr.
25	62	138	100	105	99	-	-
26	48	408	163	120	92	68	53
27	52	386	152	54	-	56	57
28	56	370	178	130	88	60	62
29	53	496	146	107	60	78	50
30	55	372	220	164	144	124	-
31	47	390	96	41	47	46	47
32	69	684	239	198	133	84	44
33	60	282	185	145	117	73	62
34	67	428	163	142	98	64	64
35	52	342	161	126	78	61	60
36	59	450	204	156	132	-	-
Average	56.7	395.5	166.9	123.8	98.9	71.4	55.4

preinjection blood sugar of the 12 calves prior to the injection of glucose was 56.7 mg/100 ml blood. The pre-injection blood sugar values ranged from 47 to 69 mg/100 ml. Following the injection of glucose the blood sugar level increased markedly with the average being 395 mg/100 ml blood at two minutes post-injection. As evidenced by this table there was considerable variation in the two minute values. This difference can be

explained by variations in injection time, by the possibility of incomplete mixing in the blood stream at two minutes, and by the variations which are found to be constant in living organisms.

After the two minute peak the blood sugar fell rapidly but in only two cases, calves 27 and 31, did it return to the pre-injection level prior to four hours. Three more of the calves, numbers 28, 34 and 35, exhibited normal blood sugar values at four hours post-injection. The remaining seven calves all showed usual blood sugar values at six hours. The most rapid fall in blood sugar in all cases occurred during the first 30 minutes as evidenced by the drop from 395 mg/100 ml at two minutes to 167 mg/100 ml at 30 minutes. Following this, the curve (Fig. 4) leveled off with normal values being assumed much more slowly.

The total blood sugar (glucose plus fructose) following the injection of fructose simulated the pattern following glucose administration (Table 2). The average pre-injection blood sugar level was 53.3 mg/100 ml blood in this instance. At two minutes post-injection the average value was 401.7 mg/100 ml blood. This figure was almost identical to the two minute average shown following glucose administration. Once more the blood sugar fell rapidly and especially during the first 30 minutes. The rate of fall once again decreased markedly after 30 minutes post-injection. In this instance calf 34 exhibited a normal blood sugar level at one hour. Calves 27, 32, 33 and 35 showed usual blood sugar values at two hours while at four hours calves 25, 26 and 29 exhibited normal readings. In three individuals a hyperglycemic condition still existed at six hours.

Table 2. Blood sugar determinations (glucose plus fructose), expressed in mg/100 ml blood, following intravenous infusion of fructose at the rate of 0.5 gm/kg body weight.

Calf	Sample time						
Number	Pre-injection	2 Min.	30 Min.	1 Hr.	2 Hr.	4 Hr.	6 Hr.
25	-	464	177	168	98	27	83
26	61	412	148	113	74	54	59
27	47	396	109	64	32	59	46
28	53	308	104	90	66	89	105
29	52	454	220	206	108	30	40
30	76	534	162	112	76	104	79
31	62	534	170	117	84	84	-
32	41	315	143	110	59	42	-
33	45	340	144	101	47	58	60
34	30	360	126	60	22	38	50
35	43	314	145	92	61	44	55
36	76	392	142	122	80	116	56
Average	53.3	401.7	149.2	112.9	67.2	62.1	63.3

The average pre- and post-injection blood fructose values prior to fructose infusion are shown in Table 3. The average pre-injection level was 5.0 mg/100 ml, indicating that some inuloid material is normally present in bovine blood. At two minutes post-injection the blood fructose values had reached a peak of 291.7 mg/100 ml. This indicated a possible rapid conversion of fructose to glucose since the average two minute total blood

Table 3. Blood fructose determinations, expressed in mg/100 ml blood, following intravenous infusion with fructose at the rate of 0.5 gm/kg body weight.

Calf Number	Sample time: Pre-injection	2 Min.	30 Min.	1 Hr.	2 Hr.	4 Hr.	6 Hr.
25	11	344	46	34	14	6	-
26	4	170	73	30	13	5	8
27	3	396	57	22	8	5	4
28	6	476	40	26	12	10	11
29	0	344	74	31	8	4	2
30	7	352	54	17	8	13	4
31	6	268	98	27	9	9	7
32	4	190	62	28	10	5	-
33	3	270	74	39	10	8	5
34	6	304	64	22	9	7	6
35	3	216	53	24	6	4	5
36	7	170	56	36	22	21	4
Average	5.0	291.7	62.6	28.0	10.7	8.1	5.6

sugar value following fructose administration was 401.7 mg/100 ml. The difference between these two figures, or 110 mg, would undoubtedly be true glucose. An even more rapid utilization of fructose is indicated as evidenced by the difference between the two minute and 30 minute values. At 30 minutes post-injection the average blood fructose level had dropped to 62.6 mg/100 ml blood. The blood fructose values continued to decrease although

Table 4. Blood sugar determinations (glucose plus fructose) expressed in mg/100 ml blood, following intravenous infusion with invert sugar at the rate of 0.5 gm/kg body weight.

Calf	Sample time						
Number	Pre-injection	2 Min.	30 Min.	1 Hr.	2 Hr.	4 Hr.	6 Hr.
25	54	402	175	146	96	40	55
26	36	576	94	58	36	36	45
27	42	346	129	96	74	83	41
28	42	396	155	112	66	55	46
29	36	382	121	68	25	32	-
30	53	332	133	113	75	63	-
31	44	360	110	47	44	53	52
32	43	600	242	122	60	46	44
33	42	524	166	110	52	38	49
34	36	492	135	98	46	47	47
35	38	456	133	86	41	49	47
36	35	500	134	86	43	43	50
Average	41.75	447	144	95	55	48.7	47.6

six hours were required for pre-injection values to be reached (Fig. 5).

The average blood sugar level in the 12 calves prior to the administration of invert sugar was 41.75 mg/100 ml blood (Table 4). This value was slightly lower than the pre-injection level previous to injection with glucose and fructose. As compared to readings following glucose and fructose injections an even

higher two minute peak was evidenced following invert sugar administration. In this instance the average two minute value was 447 mg/100 ml blood. However, the fall in blood sugar after the injection of invert sugar was more rapid as compared to glucose and fructose. There was an average decrease of 303 mg sugar/100 ml blood during the first 30 minutes post-injection. One hour following invert sugar administration the blood sugar readings of calves 26 and 31 had reached normal values. Similar levels were evidenced by seven more of the animals at two hours post-injection whereas all 12 of the calves showed normal blood sugar values at four hours. This more rapid decline in blood sugar following invert sugar infusion indicates a more rapid utilization of this carbohydrate when compared to glucose and fructose. The more rapid utilization of invert sugar could conceivably be due to the fact that fructose is more readily phosphorylated than glucose and does not require insulin for utilization (13). On the other hand, high blood fructose values apparently stimulate the production of insulin (15). Further, when invert sugar, which contains equal quantities of fructose and glucose, is infused the fructose apparently is readily phosphorylated and insulin production stimulated by both sugars thus causing a more rapid utilization of glucose.

The pre-injection blood fructose level prior to infusion with invert sugar once more showed that a small amount of inuloid material is normally present in bovine blood (Table 5). Two minute post-injection blood fructose values following the administration of a combination of glucose and fructose reached

Table 5. Blood fructose determinations, expressed in mg/100 ml blood, following intravenous infusion with invert sugar at the rate of 0.5 gm/kg body weight.

Calf Number	Sample time: Pre-injection	2 Min.	30 Min.	1 Hr.	2 Hr.	4 Hr.	6 Hr.
25	2	344	27	11	5	1	1
26	7	256	28	14	9	-	6
27	0	236	22	8	4	2	2
28	0	156	22	8	2	3	0
29	1	224	19	9	4	3	-
30	0	328	10	4	0	0	0
31	2	240	81	5	4	2	2
32	1	532	6	1	1	1	1
33	3	388	39	16	6	4	3
34	2	140	43	22	7	4	2
35	0	206	19	3	0	0	0
36	2	360	26	13	7	4	2
Average	1.7	284.2	28.5	9.5	4.1	2.2	1.7

comparable levels to those seen after fructose infusion. However the amount of fructose found in the blood assumed readings similar to those seen prior to injection by two hours post-injection as compared to the six hours required to reach usual values following the injection of fructose alone (Fig. 5).

A summary of Tables 1, 2 and 4 showing the average total blood sugar values (glucose plus fructose) and standard deviations,

expressed as mg/100 ml blood, in 12 cattle before and following intravenous infusions of glucose, invert sugar, and fructose is shown in Table 6. These values are further depicted in Fig. 4. The average blood fructose values, expressed as mg/100 ml blood, in 12 cattle before and following intravenous injections of invert sugar and fructose are shown in Table 7. These values are depicted in Fig. 5. Typical blood sugar values, as evidenced by calf 35, following the intravenous infusion of glucose, fructose, and invert sugar are shown in Fig. 6.

Urine Analysis

In the glucose treated group, an average of 194.6 grams of this sugar was administered prior to the collection of all urine formed and voided during a six hour period (Table 7). Marked diuresis was evident following the injection, and particularly during the first hour post-injection. The average urinary sugar loss in the glucose injected animals was 20.76 grams. This quantity constituted a loss of 10.92 per cent of the glucose injected.

An average of 197.2 grams of fructose was administered to the five calves prior to the collection of all urine voided from the fructose treated group (Tables 9 and 11). The resulting diuresis was comparable to that seen in the glucose infused group. Twelve and one-half grams of fructose, representing a 6.3 per cent loss of this substance, were found in the six hour urine. The loss in total sugar was 16.8 grams constituting an

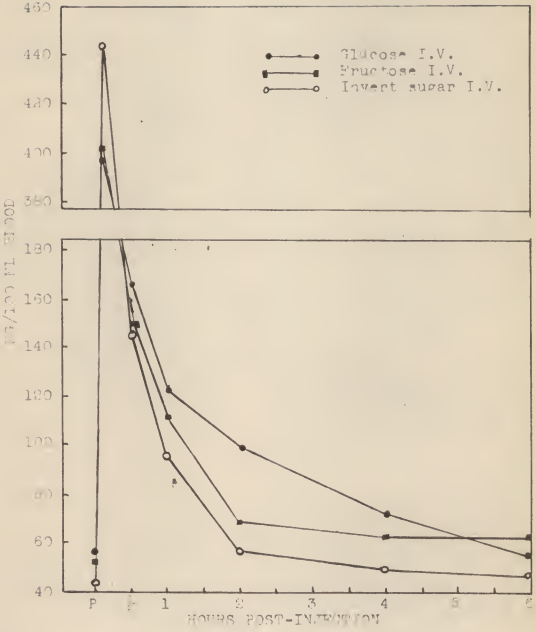

Fig. 4. Average blood sugar values of twelve calves following intravenous infusions of glucose, fructose, and invert sugar.

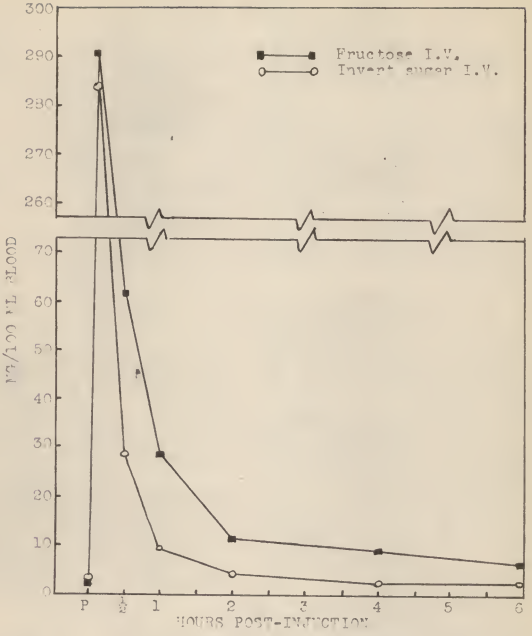

Fig. 5. Average fructose values of blood samples taken prior to and following intravenous infusions of fructose and invert sugar.

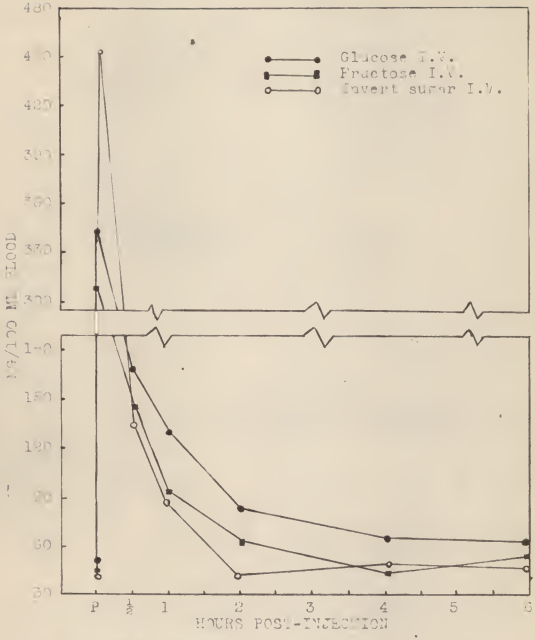

Fig. 6. Typical post-injection blood sugar values as shown by calf #35 following intravenous infusions of glucose, fructose, and invert sugar.

Table 6. Average total blood sugar values (glucose plus fructose) and standard deviations, expressed as mg/100 ml blood, in 12 cattle before and after intravenous infusions of glucose *, invert sugar *, and fructose *.

Sample Time	Intravenous infusion		
	Glucose	Invert Sugar	Fructose
Pre-injection	56.7 ± 7.0	41.7 ± 6.3	53.3 ± 14.4
2 minutes	395.5 ± 128.0	447.2 ± 90.8	401.7 ± 80.8
30 minutes	166.9 ± 43.3	144.0 ± 38.1	149.2 ± 31.2
1 hour	123.8 ± 44.4	95.2 ± 28.2	112.9 ± 40.6
2 hours	98.9 ± 30.7	55.0 ± 20.0	67.2 ± 25.2
4 hours	71.4 ± 21.5	48.7 ± 13.9	62.1 ± 29.4
6 hours	55.4 ± 7.3	47.6 ± 4.1	63.3 ± 19.8

* 0.5 gm/kg body weight.
Average weight of animals - 822 lbs.
Average amount of sugar administered - 186 gm.

8.58 per cent sugar loss. Furthermore, 4.26 grams of glucose were excreted following fructose administration. This once more indicates either a possible conversion of fructose to glucose or a preferential reabsorption of fructose over glucose in the renal tubules.

Following the administration of invert sugar, diuresis was less evident than when glucose and fructose were infused separately. Of the average of 204.8 grams of invert sugar injected, 14.66 grams of sugar were found in the urine (Tables 10 and 11). This represented a 7.3 per cent sugar loss. Since the invert sugar was prepared by mixing equal quantities of fructose and

Table 7. Average blood fructose values and standard deviations, expressed as mg/100 ml blood, in 12 cattle before and after intravenous infusions of fructose and invert sugar.

Sample Time	Intravenous infusion	
	Invert Sugar	Fructose
Pre-injection	1.7 ± 2.0	5.0 ± 2.8
2 minutes	284.2 ± 111.0	291.7 ± 95.7
30 minutes	28.5 ± 19.5	62.6 ± 15.5
1 hour	9.5 ± 6.1	28.0 ± 6.4
2 hours	4.1 ± 2.9	10.7 ± 4.2
4 hours	2.2 ± 1.6	8.1 ± 3.8
6 hours	1.7 ± 1.7	5.6 ± 3.2

glucose, each calf received identical amounts of these two sugars during the injection of invert sugar. However, even though identical amounts were administered to the same calf in the same solution, less fructose was lost via the urine as compared to glucose. This is evidenced by the fact that following invert sugar infusion an average of 8.62 grams of glucose was found in the six hour urines as compared to 6.04 grams of fructose. This indicates either a conversion of fructose to glucose, a more rapid utilization of fructose, and/or a preferential reabsorption of fructose by the kidney tubules.

A summary of Tables 8, 9 and 10 showing the average urinary sugar excretions and standard deviations of 5 cattle following the intravenous infusions of glucose, fructose, and invert sugar

Table 8. Urinary sugar excretions in six hours following intravenous infusion with glucose at the rate of 0.5 gm/kg body weight.

Total injection and Excretions	Calf number				
	26	27	31	34	35
Grams glucose injected	195	164	193	219	202
Grams glucose excreted in 6 hrs.	20.9	26.5	21.9	21.0	13.5
Grams total sugar excreted in 6 hrs.	20.9	26.5	21.9	21.0	13.5
Ml urine excreted in 6 hrs.	6700	4675	4550	5300	2800
Percentage sugar excreted in 6 hrs.	10.8	16.2	11.3	9.6	6.7

is shown in Table 11. These findings are depicted in Figs. 7, 8, 9 and 10.

An almost exact quantitative relationship existed between the amount of fructose excreted and the amount administered. This is evidenced by the fact that an average of 6.05 grams of fructose was eliminated following the injection of a 25 per cent solution of fructose (in invert sugar) and 12.5 grams were excreted following the injection of a 50 per cent solution of fructose (Table 8).

In contrast to these findings, Holmes (29), working with adult Ayrshire, Red Poll, and Shorthorn cattle, found that blood sugar values returned to normal within two and one-half hours following the infusion of glucose at the rate of 0.3 gm/kg body

Table 9. Urinary sugar excretions in six hours following intravenous infusion with fructose at the rate of 0.5 gm/kg body weight.

Total injection and Excretions	Calf number				
	26	27	28	31	33
Grams fructose injected	172	187	227	216	184
Grams glucose excreted in 6 hrs.	4.0	4.6	4.5	2.7	5.5
Grams fructose excreted in 6 hrs.	12.0	8.9	19.9	9.6	12.1
Grams total sugar excreted in 6 hrs.	16.00	13.5	24.5	12.4	17.6
Ml urine excreted in 6 hrs.	3750	5920	5525	3950	3800
Percentage sugar excreted in 6 hrs.	9.3	7.3	10.8	5.9	9.6

weight. Two to three minutes were required for this infusion. He reported the amount of sugar excreted in the urine under these conditions varied from 2.6 percent to 20.5 percent of the quantity given. The average quantity excreted was 10.3 percent. Bell and Jones (3), working with cross-bred adult Ankole and Zebu males and non-gravid heifers, injected glucose intravenously in varying amounts. Fifty percent solutions of glucose were injected at the rate of 20 ml/minute. Under these conditions it was found that 0.05 gm glucose/kg body weight was the largest amount of this sugar that could be infused in which no glycosuria occurred. When glucose was infused at rates of 0.1, 0.2

Table 10. Urinary sugar excretions in six hours following intravenous infusion with invert sugar at the rate of 0.5 gm/kg body weight.

Total injection and Excretions	Calf number				
	25	28	29	33	35
Grams invert sugar injected	212	202	222	208	180
Grams glucose excreted in 6 hrs.	8.6	16.4	4.8	4.6	8.7
Grams fructose excreted in 6 hrs.	3.3	6.1	3.4	6.3	11.1
Grams total sugar excreted in 6 hrs.	11.9	22.5	8.2	10.9	19.8
Ml urine excreted in 6 hrs.	4850	1880	1975	3840	3510
Percentage sugar excreted in 6 hrs.	5.6	11.1	3.7	5.2	10.9

and 0.5 gm/kg, these workers reported normal blood sugar values at two hours following glucose infusion with a renal threshold of 98 mg/100 ml blood. Although no attempt was made to determine the renal threshold for glucose in the present study, this reported value would seem to agree with the findings presented. This is supported by the decrease in the quantity of glucose and fructose (Tables 12 and 13) found in the urine as blood sugar values decreased. These urinary sugar values are depicted in Figs. 11 and 12.

Table 11. Average urinary sugar excretions and standard deviations of 5 cattle following intravenous infusions of glucose, invert sugar, and fructose.

Total Injection and Excretions	Intravenous Infusion		
	Glucose	Invert Sugar	Fructose
Grams sugar injected.*	194.6 ± 19.9	204.8 ± 14.3	197.2 ± 23.2
Grams glucose excreted in 6 hrs.	20.8 ± 4.7	8.6 ± 4.77	4.3 ± 1.0
Grams fructose excreted in 6 hrs.	0	6.1 ± 3.2	12.5 ± 4.4
Grams total sugar excreted in 6 hrs.	20.8 ± 4.7	14.7 ± 6.2	16.8 ± 4.8
Ml urine excreted in 6 hrs.	4805 ± 1409	3211 ± 1272	4599 ± 1047
Percent sugar excreted in 6 hrs.	10.9 ± 3.8	7.3 ± 3.5	8.5 ± 2.0

* 0.5 gm/kg body weight.

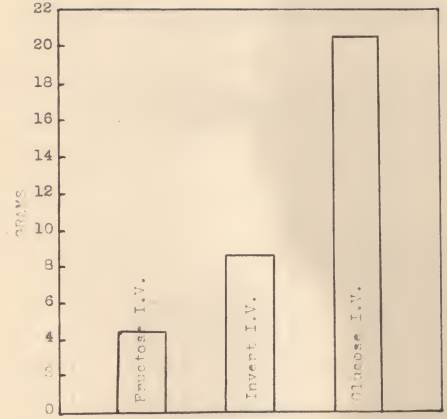

Fig. 7. Average urinary glucose eliminated by five calves in six hours following intravenous infusions of glucose, fructose, and invert sugar.

Fig. 8. Average urinary fructose eliminated by five calves following intravenous infusions of fructose and invert sugar.

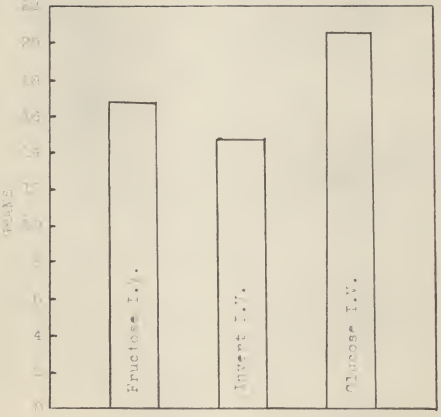

Fig. 6. Average urinary sugar eliminated by five dogs in six hours following intravenous infusions of glucose, fructose, and invert sugar.

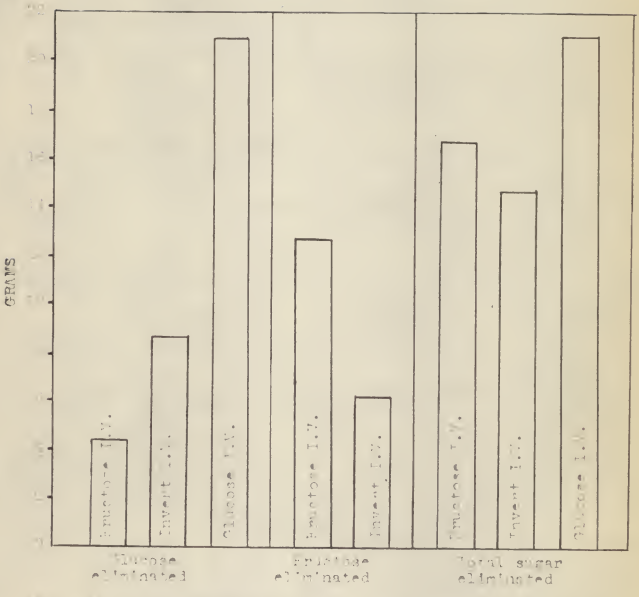

Fig. [illegible]. Average amounts of glucose, fructose, and total sugar eliminated by five calves in six hours following intravenous infusions of glucose, fructose, and invert sugar.

Table 12. Average urinary sugar, expressed in mg/100 ml urine, in 10 cattle before and after intravenous infusions of glucose, fructose, and invert sugar.

Sample	Intravenous Infusion		
Time	Glucose	Invert Sugar	Fructose
Pre-injection	0	0	0
1 hour	1099	236	467
2 hours	921	46	303
4 hours	663	74	213
6 hours	104	51	158

Table 13. Average urinary fructose, expressed in mg/100 ml urine, in 10 cattle before and after intravenous infusions of fructose and invert sugar.

Sample	Intravenous Infusion	
Time	Fructose	Invert Sugar
Pre-injection	0	0
1 hour	329	141
2 hours	150	29
4 hours	46	23
6 hours	27	10

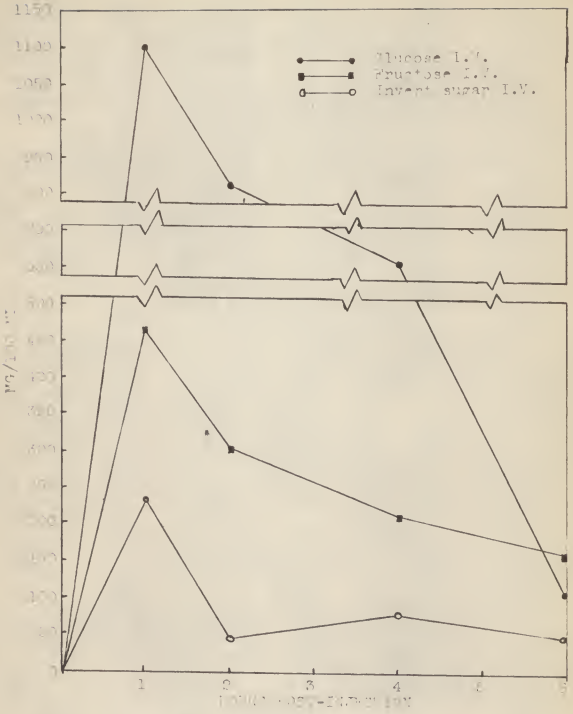

Fig. 11. Average total sugar values in urine samples taken one, two, four, and six hours following intravenous infusions of glucose, fructose, and invert sugar.

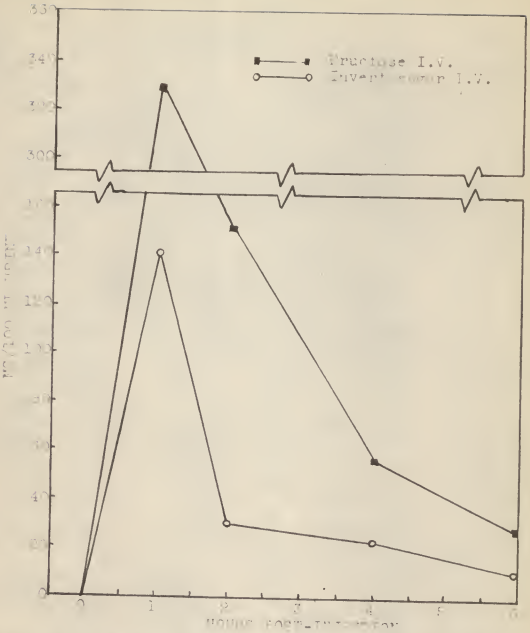

Fig. 12. Average fructose values of the samples taken one, two, four, and six hours following intravenous infusions of fructose and invert sugar.

SUMMARY AND CONCLUSIONS

1. Twelve yearling Hereford heifers were infused intravenously with equal quantities of glucose, fructose, and invert sugar at two week intervals. Blood and urine samples were collected prior to and at periodic intervals following the administration of the sugars.

2. The average blood sugar value prior to glucose injection was 56.7 mg/100 ml blood. Following the infusion the blood sugar level increased markedly and reached an average peak of 395 mg/100 ml blood. After the two minute high the blood sugar level fell rapidly but in only two cases did it return to the pre-injection levels prior to four hours and in eight of the twelve calves it required six hours for normal values to be attained.

3. The total blood sugar (glucose plus fructose) following the injection of fructose simulated the pattern shown following glucose administration. However, following fructose infusion the blood sugar values of five of the calves returned to readings within the normal range at two hours and all except three had reached the usual value at four hours post-injection.

4. When invert sugar was infused, the total blood sugar reached even higher two minute post-injection levels than when either glucose or fructose was injected separately. Following the high two minute peak the blood sugar values returned to normal levels more rapidly when compared with either fructose or glucose administration. In nine calves the values were within

the normal range at the two hour post-injection interval and all readings were normal at four hours.

5. Diuresis was marked in the calves receiving glucose and fructose but was less evident following invert sugar administration. The average urinary sugar losses expressed in per cent were 10.6, 8.5, and 7.1 following the infusion of glucose, fructose, and invert sugar, respectively. This trend was evident throughout the investigation although the high standard deviations prevented any statistical significance.

6. The results presented indicate that in the normal bovine, as in monogastric animals, intravenously administered fructose and invert sugar are more readily utilized than glucose. Further, less urinary sugar loss was found following the injection of these two sugars and especially after invert sugar. The superiority described of fructose and invert sugar in the normal animal lends support to a possible marked advantage of fructose and/or invert sugar in the treatment of cattle with ketosis.

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THE UTILIZATION OF INTRAVENOUSLY ADMINISTERED GLUCOSE, FRUCTOSE, AND INVERT SUGAR IN CATTLE

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ABSTRACT

The demonstration that insulin affected phosphorylation of glucose and that specific hexokinases for fructose and glucose existed in the liver and muscles led to investigations with fructose as a therapeutic agent in diabetes mellitus and other disturbances in carbohydrate metabolism. Later studies indicated separate metabolic pathways for glucose and fructose and that fructose metabolism was not affected in diabetes. Further investigations showed that the utilization of fructose was not dependent on insulin and that fructose was more easily phosphorylated than glucose. Other workers have demonstrated less urinary loss from intravenously administered fructose and invert sugar as compared to glucose. Direct assimilation of fructose by peripheral tissues has likewise been demonstrated. Other investigations have indicated that the rate of disappearance of glucose from the blood is slower in acidotic animals than in the normal. Thus acidosis inhibited cellular uptake of glucose and/or processes of phosphorylation. Recent work has demonstrated that fructose is ketolytic in depancreatized, ketotic dogs.

These findings suggested an evaluation of the utilization of fructose and invert sugar in cattle since it is well known that ruminants differ markedly in their carbohydrate metabolism from that of monogastric animals. Further, in case of greater advantages of these sugars over glucose, their superiority as valuable therapeutic agents would be indicated in the many disturbances of ruminants where therapy with glucose is employed and especially

in ketosis of dairy cattle.

Twelve yearling Hereford heifers fed a basal ration of cracked corn, linseed oil meal, wheat straw, salt, and vitamin A feeding oil were used in this investigation. Each calf was injected intravenously with glucose, fructose, and invert sugar in 50 per cent solutions at the rate of 0.5 gm/kg body weight at two week intervals. The invert sugar was prepared by mixing equal quantities of glucose and fructose so that the resulting solution contained 25 per cent glucose and 25 per cent fructose. The jugular vein was used as the injection site. The time required for the injection was approximately five minutes. Blood samples were obtained from the jugular vein prior to and at periodic intervals following the infusion. The post-injection samples were taken at two minutes, 30 minutes, one, two, four, and six hours following the injection. A fluoride-oxalate-thymol mixture was used as the anti-coagulant.

Urine samples were collected prior to and one, two, four, and six hours following the injection. In addition the total urine formed and voided in six hours after the infusion was collected from five calves in each group. The blood and urine samples were refrigerated immediately upon collection and protein-free filtrates prepared within three hours.

The average blood sugar value prior to glucose injection was 56.7 mg/100 ml blood. Following the infusion the blood sugar level increased markedly and reached an average peak of 395 mg/100 ml blood. After the two minute high the blood sugar level fell rapidly but in only two cases did it return to the

pre-injection levels prior to four hours and in eight of the twelve calves it required six hours for normal values to be attained.

The total blood sugar (glucose plus fructose) following the injection of fructose simulated the pattern shown following glucose administration. However, following fructose infusion the blood sugar values of five of the calves returned to readings within the normal range at two hours and all except three had reached the usual value at four hours post-injection.

When invert sugar was infused the total blood sugar reached even higher two minute post-injection levels than when either glucose or fructose was injected separately. Following the high two minute peak the blood sugar values returned to normal levels more rapidly when compared with either fructose or glucose administration. In nine calves the values were within the normal range at the two hour post-injection interval and all readings were normal at four hours.

Diuresis was marked in the calves receiving glucose and fructose but was less evident following invert sugar administration. The average urinary sugar losses expressed in per cent were 10.6, 8.5, and 7.1 following the infusion of glucose, fructose, and invert sugar, respectively. This trend was evident throughout the investigation although the high standard deviations prevented any statistical significance.

The results presented indicate that in the normal bovine, as in monogastric animals, intravenously administered fructose and invert sugar are more readily utilized than glucose. Further,

less urinary sugar loss was found following the injection of fructose and invert sugar. The superiority described of fructose and invert sugar in the normal animal lends support to a possible marked advantage of fructose and/or invert sugar in the treatment of cattle with ketosis.

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