Absolute Rates of Glucose Production, Accumulation, and Utilization in the Dog at Pancreatectomy and Thereafter

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SUMMARY

1. The method of successive measured injections of tracer has been used to determine absolute rates of glucose appearance (production), accumulation, disappearance, excretion and utilization in six fasting bitches at times before and after total pancreatectomy.
2. The rate of glucose utilization underwent a great reduction within minutes following pancreatectomy.
3. In contrast, the rate of glucose production did not change greatly at this time.
4. As a consequence, there was a rapid accumulation of glucose in the dog when measured in terms of the amount which intermixed with the injected tracer, and as seen less directly by a rise in the concentration of glucose in the blood plasma.
5. The increase in blood glucose level following pancreatectomy was accompanied by a restoration in the average rate of glucose utilization to about two thirds of its value before pancreatectomy, and by glycosuria.
6. Both the rate of production and that of utilization increased moderately during the first one or two days following total pancreatectomy. Thereafter they decreased progressively and ketonuria became severe.
7. No effect of general anesthesia (Nembutal) was noted on the above patterns of change in glucose rates.

Is overproduction or is underutilization the cause of the rapid accumulation of glucose in the body after total pancreatectomy? Are both overproduction and underutilization of glucose involved and, if so, at what stages following pancreatectomy and to what extents? Answers to these questions have been obtained in fasting bitches before the second stage of a Hédon-type operation for total pancreatectomy, and during the subsequent period of survival. The method of successive measured injections of tracer was employed, using C-14 glucose (U-L.) as a tracer.

It will be shown that an abrupt and marked fall in the rate of glucose *utilization* occurs within a few minutes after the removal of the pancreatic remnant while the rate of glucose production changes little during this period. As a result a rapid accumulation of glucose occurs in the body and the concentration of glucose in the circulating blood rises. These very early changes will be shown to be followed over a period of one or two days after pancreatectomy by a rise above normal in the rate of *production* of glucose. The rate of production, and with it the rate of glucose utilization, then decrease progressively as the terminal phase of pancreatic diabetes begins. The amount of body glucose which intermixes rapidly with added tracer remains at a high level during this final period.

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METHODS

Tracer methodology

The mathematical basis for the method of Successive Measured Injections of Tracer, which will be referred to subsequently as method SMIT, has been described and its application exemplified.[1] Rates of appearance of glucose calculated at times of tracer injection of C-14 glucose into surgically eviscerated dogs by method SMIT, have been shown to correspond closely with the measured rates of infusion of unlabeled glucose.[2,3] This close correspondence was observed when a *single* exponential function was fitted as a mathematical function relating specific activity to time after tracer injection when intermixing times were allowed to vary from fifteen to 150 minutes.

The same procedure for determining the rate R_a of appearance of glucose in the dog has been used in the experiments to be described, with intermixing times of either fifteen or thirty minutes. A value for R_a and the intermixing amount, N, of body glucose were calculated at each time of tracer injection after extrapolation to this time of fitted mathematical functions which describe as accurately as possible the change in specific activity of the plasma glucose with the time following an injection of tracer. Examples of such data following the sixth and seventh injections of tracer into the right auricle of dog number 3 are shown in figure 1. The mathematical (exponential) functions relating specific activity to time were in all cases fitted by an IBM 7090 computer.* Values of R_a and N calculated at these and at all other times of tracer injection in this experiment by method SMIT are shown in figures 2 and 3a, respectively.

Having obtained a series of calculated values for N at a set of accurately measured times, the increase ΔN in the amount of intermixing glucose in the time interval Δt between any two successive times of tracer injection was calculated. The quotient of these two values, $\frac{\Delta N}{\Delta t}$, represents the average rate of accumulation of glucose in the experimental subject during that time interval. This rate of accumulation represents at all times the difference between the corresponding rate of glucose appearance R_a in the subject and the rate of its disappearance R_d from the subject. Stated mathematically:

$$\frac{\Delta N}{\Delta t} = R_a - R_d \qquad (1)$$

The values for $\frac{\Delta N}{\Delta t}$ derived from the values in figure 3a are shown in figure 3b using values for ΔN and Δt determined by the procedures described above. The corresponding value for R_d can then be calculated by Equation 1.

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TYPICAL VARIATION WITH TIME IN VALUES OF SPECIFIC ACTIVITY AND PLASMA GLUCOSE LEVEL FOLLOWING TRACER INJECTION

Values for the rate of appearance and the amount of intermixing body glucose at times of tracer injection are calculated from these data.

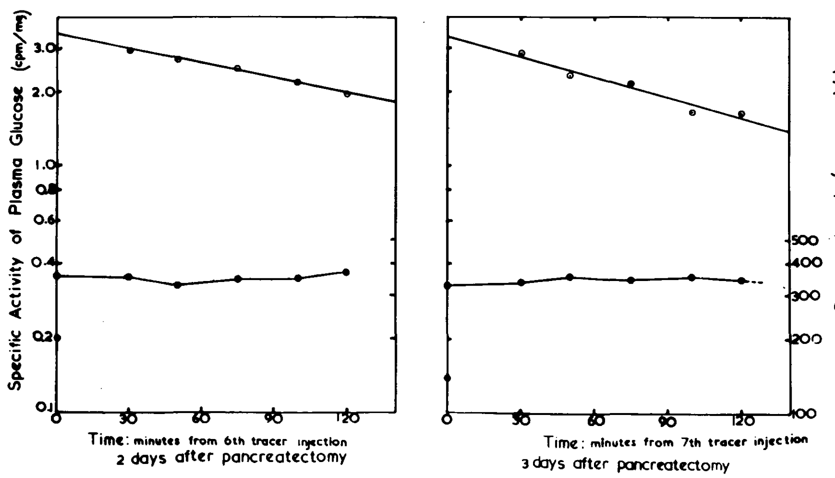


FIG. 1. Typical variation with time in values of specific activity and level of plasma glucose following tracer injection. Values for the rate of appearance and the amount of intermixing body glucose at times of tracer injection are calculated from these data.

VARIATION WITH TIME IN RATE OF APPEARANCE (PRODUCTION) OF GLUCOSE R_a BEFORE AND AFTER TOTAL PANCREATECTOMY IN DOG No. 3

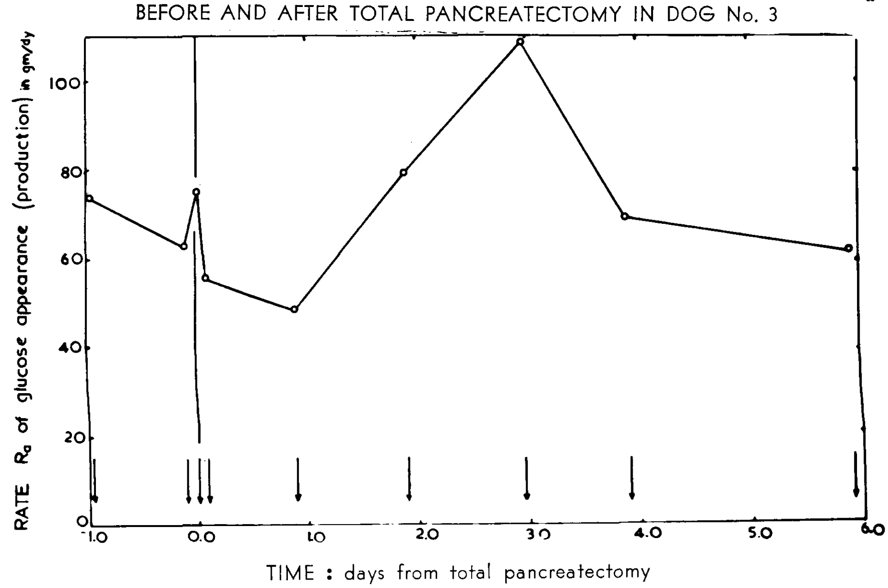


FIG. 2. Variation with time in rate of appearance (production) of glucose R_a, before and after total pancreatectomy in dog No. 3. Arrows indicate times at which a measured amount of C-14 glucose was injected intracardially.

VARIATION WITH TIME BEFORE AND AFTER TOTAL PANCREATECTOMY IN INTERMIXING AMOUNT, N, OF BODY GLUCOSE [——], IN FASTING GLUCOSE LEVEL [----] (TOP) AND IN THE CORRESPONDING RATE OF GLUCOSE ACCUMULATION $\frac{\Delta N}{\Delta t}$ (BOTTOM) IN DOG No. 3

Arrows indicate times at which a measured amount of C-14-glucose was injected intracardially

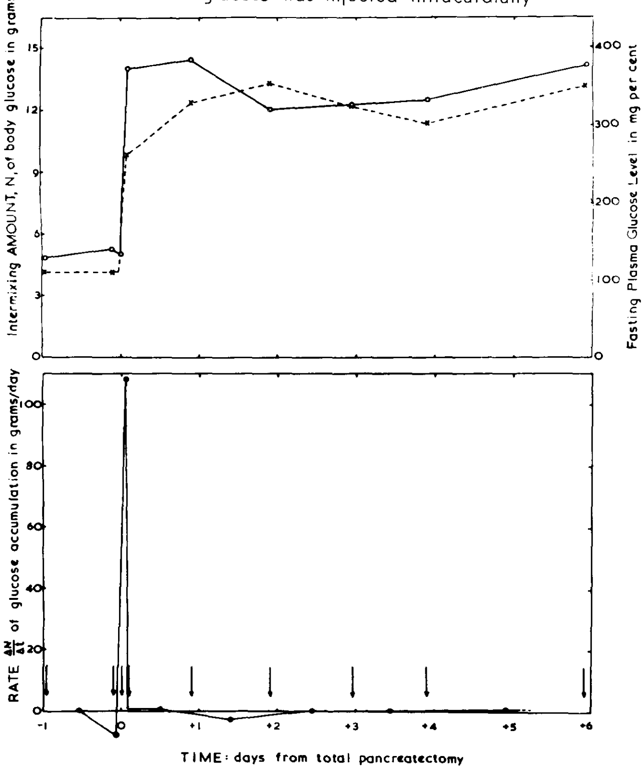


FIG. 3a. Variation with time before and after total pancreatectomy in the intermixing amount N of body glucose and in the fasting plasma glucose level in dog No. 3.
FIG. 3b. Variation with time before and after total pancreatectomy in the corresponding rate of glucose accumulation in dog No. 3.

Quantitative values for the rate of excretion of glucose into the urine, R_{ex}, were measured daily for each subject. From R_d and R_{ex} daily values for the rate of *utilization* of glucose, R_u by the subject were calculated by the equation: $R_u = R_d - R_{ex}$ (2)
Such a calculation is exemplified for dog Number 3 in figure 4, in which the values shown for R_d were calculated by Equation 1.

Treatment of animals

The subjects were mongrel bitches weighing ten to seventeen kilograms. The four unanesthetized dogs were trained to stand in a Pavlov harness or to lie quietly and did so during the subsequent periods of tracer injection and collection of blood samples. Each dog was depancreatized in two stages using a modification of the Hédon procedure.[4,5] The first stage of the partial pancreatectomy was performed under general anesthesia (Nembutal, 30 mg. per kilogram, intravenously). The duodenal and splenic portions of the pancreas were dissected free and resected, care being taken to remove all remnants of pancreas from the areas of dissection. The uncinate process of the pancreas, which is supplied and drained by the ileocolic artery and vein, was left in situ. This remnant was passed through a hole made in the muscular wall of the abdomen and was anchored subcutaneously. The open end of the small pancreatic duct draining the remnant was exteriorized.

Four days later the second and final stage of the total pancreatectomy was performed between two determinations of R_a and N. This final stage of total pancreatectomy and subsequent tracer studies were done in two dogs under general anesthesia (Nembutal) and in four dogs under local anesthesia (Procaine).

In using tracer method SMIT, the injections of C-14 glucose were made into the right auricle by means of an indwelling polyethylene cannula placed in the left external jugular vein. Blood samples also were drawn from the right auricle, the volume of blood removed being replaced by an equal volume of a 0.9 per cent aqueous solution of sodium chloride. During such experimental periods each conscious animal was placed in a polyethylene bag, with holes for head and legs, designed to catch urine which otherwise would have been lost. At other times the animal was kept in a metabolism cage, the urine being collected quantitatively each day at recorded times from the clean polyethylene catch-basin in which sodium fluoride had been placed.

Chemical and physical analyses

Each urine sample was tested qualitatively for ketone bodies (Ketostix), protein and glucose (Uristix), blood (Hemastix), and quantitatively for glucose.[6] For three of the six animals the glucose concentration in samples of blood plasma was determined by Somogyi's modification[7] of the method of Nelson,[8] using plasma filtrates deproteinized according to Somogyi.[9] Glucosazone precipitates were prepared from other aliquots of the plasma filtrate and from standard dilutions of the solution of tracer glucose, for the determination of radioactive strengths using an automatic windowless flow counter (Tracerlab).

In the other three animals, plasma glucose concentrations were determined by glucose oxidase, using the procedure of Hugget and Nixon.[6] The radioactive strengths of C-14 in glucose eluted by paper chromatography from samples of plasma[10] were measured as indicated above. From these determinations the specific activity of the glucose in each sample of plasma was

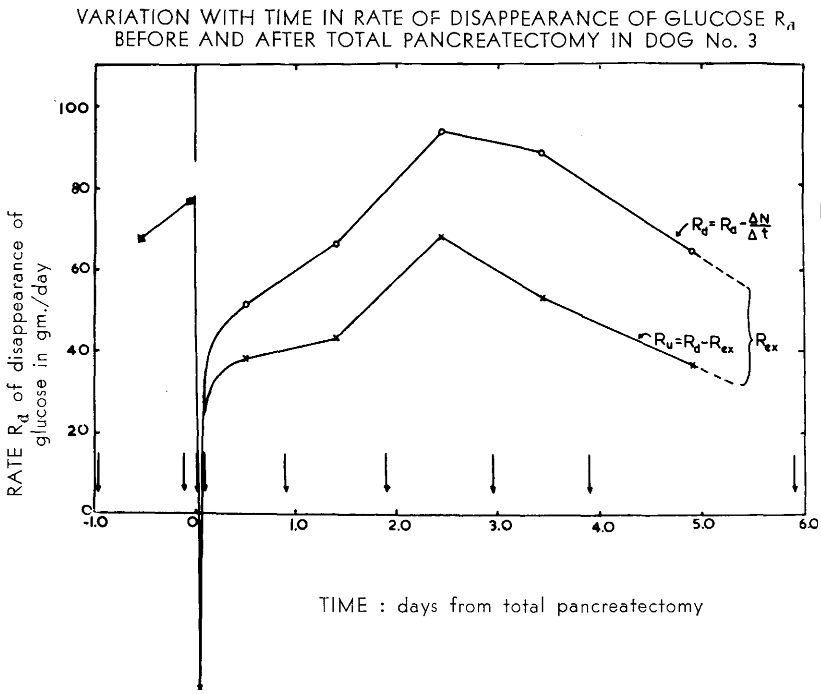


FIG. 4. Variation with time before and after total pancreatectomy in glucose rates R_d (disappearance), R_{ex} (excretion in the urine), and R_u (utilization) in dog No. 3.

calculated as counts per minute per milligram of plasma glucose.

RESULTS

A general outline of the experiments is given in table 1. Concurrent changes in the fasting plasma glucose level and in the rates of glucose appearance, accumulation, disappearance, utilization and excretion are shown in figure 5 for animal number 3. To form this figure the data of figures 2, 3 and 4 were combined using average values for R_a between successive times of tracer injection. Similar composite rate diagrams for dogs 2, 5 and 6 are shown in figures 6, 7a and 7b. To permit closer comparisons, the observed rates of endogenous glucose production before and following pancreatectomy have been expressed as grams of glucose per day per kilogram of body weight and are plotted as functions of the time from pancreatectomy in figure 8 for all animals.

In dog No. 1 the calculated rate of appearance *fell* from 67.9 gm. of glucose per day at 1.25 hrs. before pancreatectomy to 54.5 gm. per day at 1.92 hrs. after pancreatectomy. The times stated are those of the first and second tracer injections. The amounts of body glucose with which the injected tracer glucose intermixed at the above two times were 4.09 and 8.11 gm., respectively.

Using the average of the above rates of appearance (61.2 gm. glucose per day) and the average rate of accumulation of glucose *following* pancreatectomy (50.1 gm. glucose per day), the corresponding rate of disappearance was 11.1 gm. of glucose per day by Equation 1. The conclusions from these calculations, using method SMIT, are: (1) that during the first two hours following pancreatectomy, glucose accumulated

TABLE 1

General characteristics of experiments

Animal Number	Sex	Breed	Initial body weight (kg.)	Days between first and second stage pancreatectomy	Anesthetized or conscious	Minutes of handling at pancreatectomy	Blood glucose rise during handling (mg. per 100 ml.)	Days post-pancreatectomy	Number of tracer injections	Terminal condition of dog
1	F	Beagle	10.3	3	A	—	—	2	3	Good
2	F	Mongrel	13.3	4	A	—	—	5	8	Good
3	F	Hound	17.3	4	C	26	0	7	9	Coma
4	F	Beagle	9.6	4	C	24	2	1	4	Anemia after massive hemorrhage
5	F	Hound	14.8	4	C	21	15	4	7	Proteinuria and vomiting
6	F	Hound	10.3	4	C	41	28	3	6	Signs of slow hemorrhage

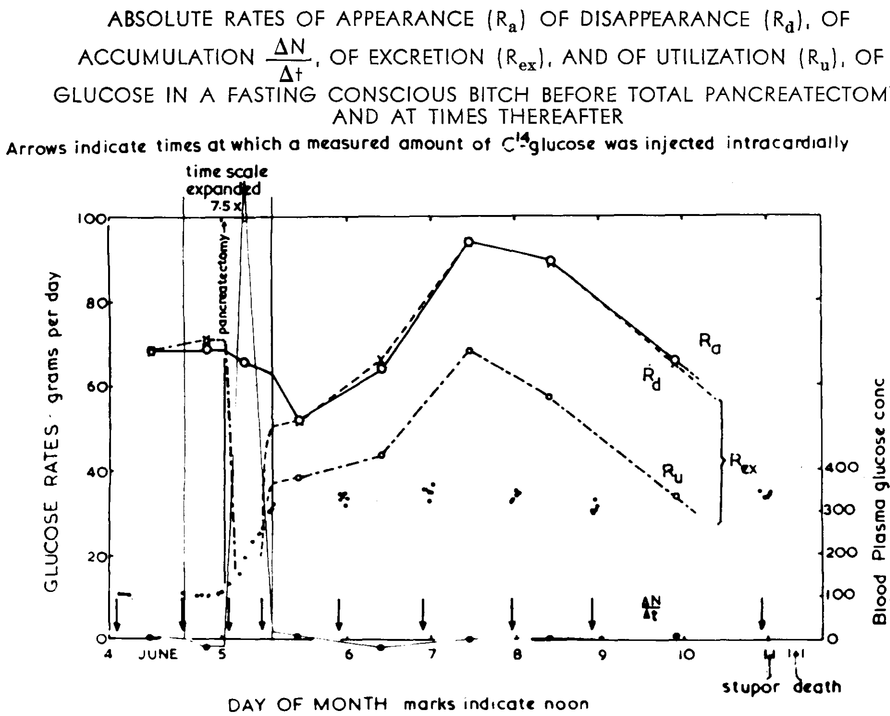


FIG. 5. Absolute rates of appearance, R_a, of accumulation, $\frac{\Delta N}{\Delta t}$, of excretion, R_{ex}, of disappearance, R_d, and of utilization, R_u, of glucose in fasting conscious dog No. 3 before total pancreatectomy and at times thereafter. Plasma glucose concentrations are shown as well.

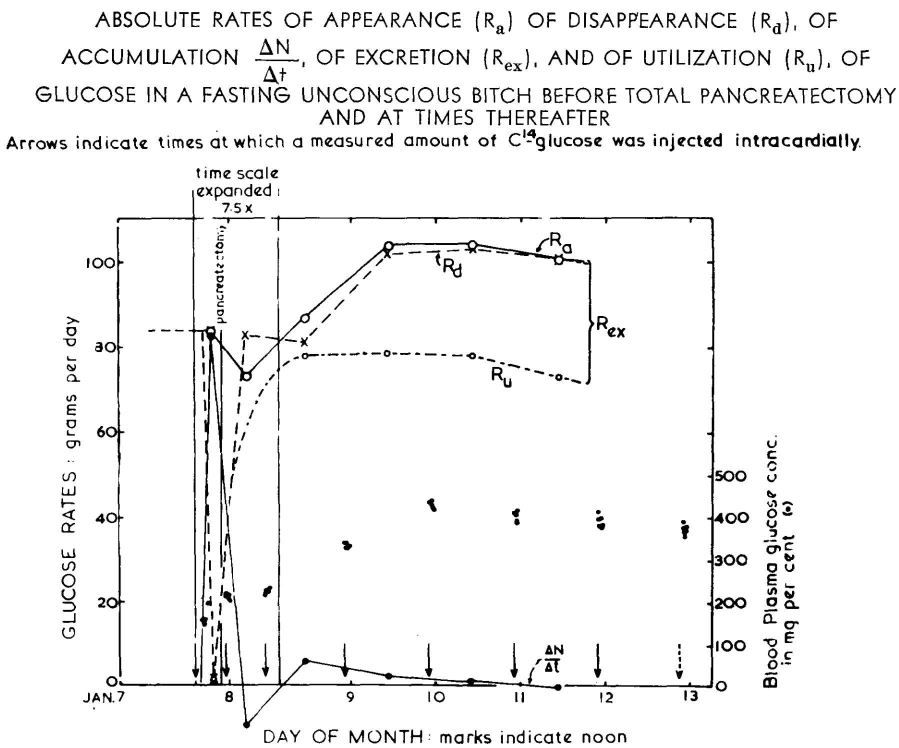
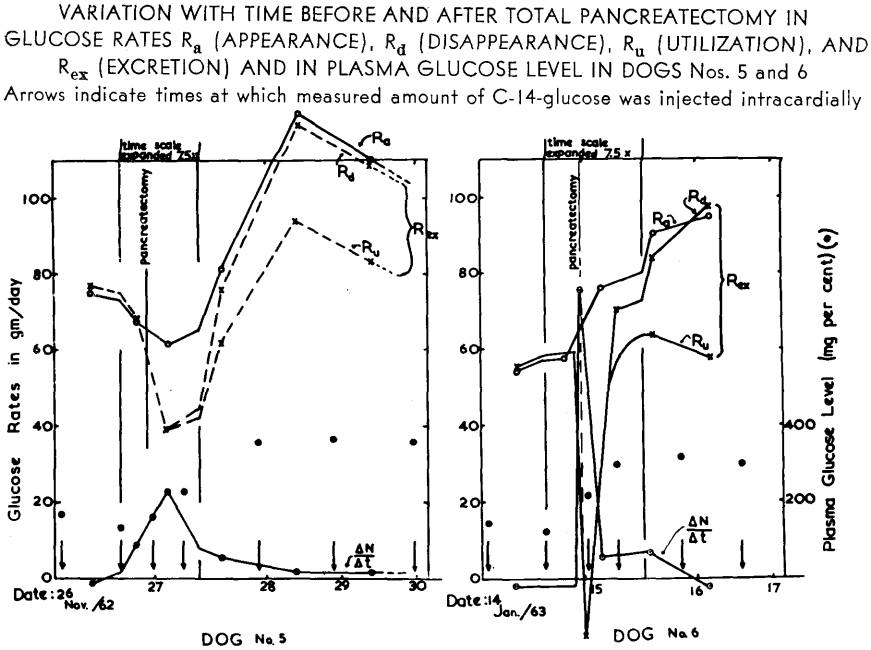


FIG. 6. Absolute rates of appearance, R_a, of accumulation, $\frac{\Delta N}{\Delta t}$, of excretion, R_{ex}, of disappearance, R_d, and of utilization, R_u, in fasting anesthetized dog No. 2 before total pancreatectomy and at times thereafter. Plasma glucose concentrations are shown as well. Data collected following the last tracer injection were not used in calculations because the cannula ligature was found to be loosened.

in dog No. 1 due to an average fall in rate of utilization to less than one fifth of its value when the stump of pancreas was in circulation; (2) that no simultaneous rise in rate of glucose production was detected.

The same conclusions can be reached qualitatively by inspection of the data for dog No. 1. The accumulation of glucose was virtually complete before the second injection of tracer glucose was made at 1.92 hrs. *following* pancreatectomy. However, the specific activity of the body glucose just prior to this second in-



FIGS. 7a, 7b. Variation with time before and after total pancreatectomy in glucose rates R_a (appearance), $\frac{\Delta N}{\Delta t}$ (accumulation), R_d (disappearance), R_u (utilization), R_{ex} (excretion) and in plasma glucose concentrations in conscious dogs Nos. 5 and 6, respectively.

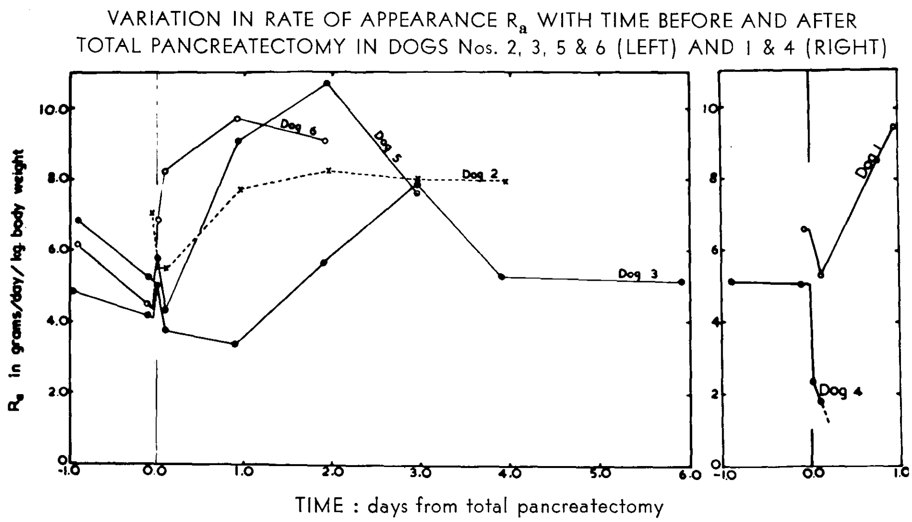


FIG. 8. Comparison in rates of glucose appearance per kilogram of body weight for all dogs before and after pancreatectomy.

jection fell close to the exponential decay curve relating the specific activity of plasma glucose to the time following the first tracer injection which was made *before* pancreatectomy. Had the rate of glucose production been increased appreciably by the pancreatectomy the specific activity of plasma glucose just before second tracer injection would have been much lower. Since it was not, it follows again that most of the accumulation of body glucose immediately following pancreatectomy resulted from decreased utilization rather than overproduction of glucose in this animal. This initial experiment of the series was terminated at one day following pancreatectomy to permit assessment at autopsy of the surgical procedures, which were found to be satisfactory. That underutilization rather than overproduction of glucose was the main cause of the *initial* accumulation of glucose following pancreatectomy in each of the six bitches studied in this series is apparent in composite figures 5, 6, 7a and 7b for animals 2, 3, 5 and 6, respectively. Each of these dogs survived for days following pancreatectomy.

Of particular interest in this regard is the experiment on dog Number 4. In this animal the single ligature which had been placed around the artery which had supplied the pancreatic stump slipped off, resulting in a massive hemorrhage which proved fatal several hours later. Three lines of evidence indicate that this accident occurred within the first hour following the second stage of pancreatectomy. The occurrence of a state of weakness and drowsiness of sudden onset, a significant fall in the ratio of packed cell volume to blood volume and slight oozing of fresh blood at the site of the incision, all were noted at nearly the same time: fifty-two minutes following pancreatectomy. At autopsy, 280 ml. of blood were recovered from the abdomen, and the loss of the ligature was confirmed.

In spite of this development, the amount of body glucose and the plasma glucose concentration in this animal *rose* progressively within minutes after pancreatectomy, even though the hemorrhage caused the endogenous rate of glucose production to fall precipitously, first to 43 per cent, then to 35 per cent of its value before pancreatectomy (figure 8). According to Equation 1 *accumulation* of glucose under this circumstance must have resulted from even greater decrease in rates of glucose disappearance and utilization.

The effects of the massive hemorrhage and of pancreatectomy in the above dog on the rates of glucose production and utilization remain unresolved, except through comparisons of such rates in this animal with those seen in the other five animals.

Returning to a comparison of figures 2 and 3, as well as to an examination of figures 5, 6, 7a and 7b, it is apparent that, as the *concentration* of glucose in the plasma rose progressively above its normal level, the rate of glucose utilization also increased. However, due to the excretion of glucose from the body at the elevated blood glucose levels the hyperglycemia did not reach a sufficiently high level to restore the rate of glucose utilization to a normal value.

Early changes in the rate R_a of appearance of glucose following pancreatectomy at best played only a minor part in the resulting accumulation of body glucose. Nevertheless, the observed changes are of special interest, particularly so because tracer method SMIT was shown to provide both valid and accurate rates of glucose appearance in the dog.[2,3] In all four subjects where more than one determination was made before pancreatectomy there was a progressive fall in R_a with increasing duration of fasting. There was an average *increase* of 21 per cent in R_a when determined within fifteen to twenty-seven minutes after pancreatectomy in dogs 3, 5 and 7. This increase was transient in dogs 3 and 5 (figure 8). A *decrease* of 20 per cent in R_a was observed at this time in dog number 2, and of 57 per cent in dog number 4 in which the massive hemorrhage occurred.

Within one day after pancreatectomy there was a rise in R_a in all cases. This rise passed through a peak at from one to three days following pancreatectomy, decreasing thereafter in each of the four subjects surviving through this period. This late decrease in rate of glucose production was accompanied by a fall in rate of glucose utilization (figures 5 and 6). Ketonuria was first detected at about one day after pancreatectomy, and progressed to high (4+) concentration by the third day in dogs 2 and 3.

An undesirable complication was introduced into three of the four experiments with unanesthetized dogs. This consisted of an elevation in the plasma glucose level during the handling of these dogs just before the second stage of pancreatectomy. Handling involved the holding of the dog in a suitable position for the injection of the local anesthetic as well as for the minor surgery involved at the second stage of total pancreatectomy. The extent of the increases in plasma glucose level at this period is indicated in table 1 for the four dogs studied without general anesthesia.

Of the six animals, only Number 3 died in a comatose state. At the time of the final injection of tracer it showed the signs of drowsiness, somnolescence, lethargy and ataxia seen in comatose animals.[11] The last tracer injection was made at approximately nine hours before the death of this animal.

Historical aspects of the overproduction-underutilization controversy have been critically reviewed by Soskin and Levine.[12] The need for experimental methods which would provide *total* rather than *net* rates of glucose production and utilization on which to judge the merits and shortcomings of glucose overproduction and underutilization is to be seen repeatedly in Chapters VIII-XIV of this monograph. Using tracer method SMIT, such total rates have been obtained and are reported in this paper.

The consistent pattern of an abrupt and very large decrease in the total rate of glucose utilization, observed within a few minutes after total pancreatectomy, is in agreement with that described for the initial action of injected insulin in both diabetic and normal dogs.[13-15] In these earlier tracer studies the injection of extracted and purified insulin resulted in an abrupt and large increase in the rate of glucose utilization. The *opposite* effect in the present experiments, following quickly on the complete *removal* of the source of insulin, is of even greater physiological significance. This is so since reservations concerning possible side-effects of injecting insulin from animals of a different species and possible chemical changes in the hormone during its extraction and purification are eliminated.

General anesthesia produced by Nembutal in dogs 1 and 2 did not alter the initial effect of pancreatectomy on the rate of glucose utilization, R_u, as seen in unanesthetized dogs 3 to 6. The similarity of this effect in anesthetized dog 2 and unanesthetized dog 3 can be seen by comparing figures 5 and 6.

The calculated fall in R_u just following pancreatectomy was so great in conscious dogs 3 and 6 that *negative* values were obtained. Since negative values for R_u are physically impossible, the potential causes of these anomalous results must be considered.

The values for R_u were calculated in terms of R_a and $\frac{\Delta N}{\Delta t}$ by Equation 1. Since tracer method SMIT was validated for values of R_a, the probable source of the anomaly is in the term $\frac{\Delta N}{\Delta t}$. Since the time interval Δt was measured accurately, the difficulty appears to be localized to the determination of ΔN.

Inaccuracies in ΔN could reflect an inability of tracer method SMIT to provide accurate values of N. The reliability of values for the amount N of the glucose in the dog which intermixes with injected tracer glucose remains to be shown. However, it has been shown, using the same method in diabetic human subjects, that the absolute amount of unlabeled glucose injected intravenously can be determined with reasonable success,[16] the differences between the measured and tracer-determined injected amounts in two tests being —5.7 per cent and +2.5 per cent.

Errors in ΔN also could result from the combined effects of excitement and alarm in conscious dogs 3 and 6 associated with the injections of local anesthetic and the subsequent removal of the pancreas stump. In dog 6 these "handling" activities caused an appreciable elevation of the plasma glucose level *before* pancreatectomy was accomplished (table 1). If this prepancreatectomy rise in blood glucose level was accompanied by a corresponding increase in N, the contribution to ΔN during this period would be sufficient to account for the negative value in R_u calculated for dog 6. All values of ΔN across the time of pancreatectomy were calculated on the assumption that the entire increment occurred in the time between pancreatectomy and the time of the next injection of tracer.

There was no detectable rise in the plasma glucose level of dog 3 during the period of handling associated with pancreatectomy (table 1). However, in this animal pancreatectomy was followed by a transient rise in R_a (figure 2). Since *average* values of R_a for each time interval between successive injections of tracer were used in the calculations of R_u by Equation 1, it can be seen (figure 5) that this transient increase in R_a was obliterated, making the calculated value of R_u too low (negative).

This inherent limitation of tracer method SMIT was acknowledged when the method was first described.[1] At the same time the experiments reported in this paper show, without exception, that a great reduction occurs in the rate of glucose utilization following pancreatectomy in the dog.

This great reduction, observed within one-half hour following pancreatectomy in the five dogs in which it was sought, raises questions concerning the possible physiological roles of the "free" and "bound" insulin moieties said to exist in the circulating blood. It has been noted[17] that an effect of a moderate degree of hyperglycemia in nondiabetic human subjects is to cause most of the "bound" inactive insulin in the circulating blood to be transformed to the "free" and effective form within a ten-minute interval. The possibility arises that such a shift, rather than increased secretion of insulin by the pancreas, is a rapid mechanism in the nondiabetic animal by which a rise in blood glucose level is reduced by insulin. If this is so, then the shift from "bound" to "free" native insulin in the blood of the freshly depancreatized dog should prevent for a finite time or should reduce the observed large fall in rate of glucose utilization and consequent accumulation of glucose in the blood plasma. This point is being explored by observing the effect of pancreatectomy on R_d at very short times between the second stage of total pancreatectomy and subsequent injection of tracer.*

*Since this paper was submitted, results have been obtained from one such experiment by Dr. M. Vranic and the authors. The plasma glucose concentration was rising at four minutes after clamping off the artery and vein subserving the pancreatic remnant of a fasting, partially depancreatized dog. The continuous rise during forty-nine minutes was from 101 mg. per 100 ml. into frank hyperglycemia (197 mg. per 100 ml.). The apparent glucose space had not changed perceptibly at thirteen minutes after clamping. At this time the rate of production of glucose had increased to 5.32 gm. per hour from a value of 2.31 gm. per hour before clamping. Between the same two times the rate of utilization had decreased from 2.31 to 0.78 gm. of glucose per hour.

These results confirm the rapid effect of pancreatectomy on the rate of glucose utilization reported in this paper. They also indicate that the initial and transient effect of pancreatectomy on the rate of glucose production is larger than was observed using the rather ponderous and slow method SMIT. They indicate the importance of the continuous secretion of insulin in preventing the development of hyperglycemia in the fasting partially depancreatized dog. The concept of a transformation from "bound" to "free" insulin in the blood plasma is not supported by our observations.

Whether or not the very transient rise in R_a, observed in two of the conscious dogs at sixteen and twenty-five minutes after pancreatectomy represents a direct response of the liver to stoppage of insulin secretion is a matter for speculation. In this regard it may be of interest to note that the average ability of the partially depancreatized dog of this series to ingest foods containing carbohydrate and protein without resulting hyperglycemia was very limited, even though the fasting blood glucose level was within the normal range. Their ability to store liver glycogen may have been correspondingly reduced.

For periods of as long as one day following total pancreatectomy, changes of any type in the rate of glucose appearance represented only small fractions of the value determined just preceding pancreatectomy in four of the five uncomplicated experiments (figure 8). Since experiments on liverless dogs indicate that over 70 per cent of the endogenous glucose in fasting dogs is hepatic in origin,[18] this feature of liver function was neither immediately nor extensively affected by the removal of the endogenous source of insulin.

Using the method SMIT variations with time in values for the quotient:

$$Q = \frac{\text{(intermixing amount of body glucose)}}{\text{(concentration of glucose in venous plasma) (body weight)}}$$

which sometimes is expressed as a per cent and referred to as the glucose space, can be calculated at each time of tracer injection. Q showed no recognizable pattern of change in the present experiments, either within one hour following pancreatectomy or thereafter.

SUMMARIO IN INTERLINGUA

Valores Absolute del Production, Accumulation, e Utilisation de Glucosa in le Can

1. Le methodo de successive injectiones de mesurate quantitates de traciantes esseva usate pro determinar le valores absolute del apparition (production), accumulation, disparition, excretion, e utilisation de glucosa in sex jejunante canes-femina a varie periodos ante e post pancreatectomia total.

2. Le utilisation de glucosa esseva grandemente relentate intra minutas post le pancreatectomia.

3. Del altere latere, le production de glucosa non se alterava significativemente a iste tempore.

4. Per consequente, il occurreva un rapide accumulation de glucosa in le can, a judicar per le mesura del quantitate intermixte con le injicite traciante. Le mesme facto esseva manifeste in le augmentate concentration de glucosa in le plasma del sanguine.

5. Le augmento del nivello de sucro de sanguine post pancreatectomia esseva accompaniate de un restauration del utilisation medie de glucosa a circa duo tertios de su valor ante le pancreatectomia e del supervenientia de glycosuria.

6. Tanto le production como etiam le utilisation de glucosa se intensificava moderatemente durante le prime un o duo dies post pancreatectomia total. Postea le duo valores declinava, e cetonuria deveniva sever.

7. Esseva notate nulle effecto de un anesthesia general (con Nembutal) super le mentionate alterationes.

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