Splanchnic retention of intraduodenal and intrajejunal glucose in healthy adults

G. Livesey, P. D. G. Wilson, M. A. Roe, R. M. Faulks, L. M. Oram, J. C. Brown, J. Eagles, R. H. Greenwood, and H. Kennedy. Splanchnic retention of intraduodenal and intrajejunal glucose in healthy adults. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E709–E716, 1998.—Estimates of splanchnic retention and appearance in the systemic circulation of orally administered glucose vary among laboratories even after recently identified sources of error have been accounted for [Livesey, G., P. D. G. Wilson, J. R. Dainty, J. C. Brown, R. M. Faulks, M. A. Roe, T. A. Newman, J. Eagles, F. A. Mellon, and R. Greenwood. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E717–E728, 1998]. We questioned whether, in healthy humans, D-glucose delivered intraluminally to the midjejunum appeared systemically as extensively as that delivered intraduodenally. Subjects were infused over a period of 90 min with 50 g of glucose in 1 liter of isotonic saline (incorporating 0.5 g D-[13C6]glucose) per 70 kg of body weight. Infusions were via enteral tubes terminating at 15 and 100 cm postpylorus. The systemic appearance of glucose was monitored by means of a primed-continuous intravenous infusion of D-[6,6-2H2]glucose. Whereas 98 ± 2% (n = 7) of the duodenally infused glucose appeared in the systemic circulation, only 35 ± 9% (n = 7) of midjejunally infused glucose did so, implying that 65 ± 9% was retained in the splanchnic bed. Either glucose was less efficiently absorbed at the midintestinal site or hepatic glucose sequestration was increased 10-fold, or both. The proximal intestine plays a key role in the delivery of glucose to the systemic circulation, and the distal intestine potentially delivers more glucose to the liver.

Little is known about the systemic appearance of glucose that arrives in the distal intestinal lumen, yet this potentially happens during the consumption of slowly digestible starches, during the congestion of either motility or osmotic agents, and when pancreatic secretions are inadequate. Moreover, the distal small intestine is important in individuals who have had their proximal intestine surgically removed for health reasons. The extent to which orally administered glucose is absorbed and escapes hepatic sequestration to reach the systemic circulation in humans can be determined using dual isotope methodology (3, 9, 11, 13). In people with a healthy intact small intestine, experimentally determined values range from 70 to 95% or more (for an analysis see Ref. 9). In many instances, low estimates can be explained quantitatively by choice of a too-small effective-pool volume, through which the glucose becomes distributed after absorption, and a too-infrequent blood sampling for adequate kinetic analysis, particularly in the early, rapid phase of glucose absorption (9). But these did not explain all the low systemic appearance estimates published that followed the use of dual isotope methodology. Known physiological causes of low systemic glucose appearances in healthy people are few. Potential causes are either incomplete absorption of glucose, which is then either retained intraluminally or fermented after passage to the large intestine, or the sequestration of glucose during its first passage through the liver to which it is first directed via the portal vein. The potential for poor absorption exists if glucose can escape the proximal small intestine, where the density of glucose transporters is high relative to the distal small intestine (2, 4). Poor absorption in the distal section of the small intestine would happen only if glucose transporters were rate limiting. It was therefore of interest to test the hypothesis that the extent of systemic appearance of glucose depends on the site at which glucose is delivered to these sites using the dual stable isotope approach (9). An appendix is given to facilitate an understanding of the modeling methodology used in the oral glucose load dual stable isotope paradigm, to avoid confusion with other experimental paradigms and to give background, details of augments, and important aspects of the glucose modeling methodology, which if included in the body of the paper would cause diversion from the central thrust.

METHODS

Participants. Nine healthy volunteers with no history of gastrointestinal disease were recruited. Six were female, three were male; they were 43 ± 11 (27–57) yr old, weighed 71 ± 13 (48–91) kg, and had a body mass index of 24 ± 3 (19–28) kg/m². They ate their habitual diets, were weight stable between recruitment and performance of investigations, and were nonmedicated. Informed written consent was provided by all volunteers, and the study was approved by the ethics committees of the Institute of Food Research and the Norfolk and Norwich Health Authority.

Experimental design. Volunteers were oroenterally intubated 48 h before investigations. The enteral tube was 1.5 mm OD, 0.75 mm ID, PVC (Portex, Hythe, UK) fitted through a terminal pear-shaped 10-g stainless steel weight (Institute of Food Research, Norwich, UK). Food and nonalcoholic drinks continued normally while the tube was being posi-
tioned and was in place. An internal length of tube equal to the mouth-to-ear-to-2nd-rib distance plus 15 cm was placed for intraduodenal delivery (15 cm postpylorus), and this length of tube plus ~85 cm was placed for the midjejunal site (100 cm postpylorus). Entry into the duodenum was ascertained with a neutral bile-containing aspirate and stethoscopic location of air delivered through and bubbled from the tube. The midjejunal location was established by fluoroscopy (BUPA Norwich, Colney, Norwich, UK). From the pool of nine volunteers, seven were duodenal and seven were midjejunal. For those who were intubated twice, the procedures were ~6 wk apart.

In the 12 h before each investigation, the subjects had no food and only water to drink. The volunteers rested overnight before being seated for 10 h in a redliner chair (Parker Knoll, UK). An antecubital vein and a subsequently heated (41°C) dorsal hand vein were cannulated (18-g Teflon) and kept patent with physiological saline. Pyrogen-free D-[6,6-2H2]glucose (99 mol% enrichment, C/D/N Isotopes, K&K Greeff, Croydon, UK) was administered as a primed (500 mg, 10 ml aqueous solution) continuous (6 mg/min as a 68.5 g/l aqueous solution) infusion into the antecubital vein, starting at ~0900, which is denoted time 0 in RESULTS. After 2 h, we enterally infused 50 g D-glucose [labeled with 500 mg D-[13C6]glucose (99 mol% enriched, also C/D/N Isotopes)] in 1 liter of isotonic NaCl over a period of 90 min. Arterialized venous blood was drawn into tubes from the heated hand initially at 15-, then at 30-, and then at 60-min intervals, as indicated in Figs. 1–6.

Glucose and isotope analysis. Plasma glucose was determined by use of hexokinase, and plasma glucose isotopes were determined on butylboronic acid derivatives by use of gas-chromatography electron impact mass spectrometry. The details of these procedures and the precision of the methods were as we described previously (9).

Rate of appearance calculations and statistics. The rate of appearance (Ra) of enterally intubated glucose was estimated using a one-compartment model that has been identified to be suitable in the present experimental paradigm (see Ref. 9 and APPENDIX) and applies an effective glucose distribution volume of 230 ml/kg body weight (9). Details of this approach and justification of the use of the one-compared with a two-compartment model in the present experimental paradigm are as given before (9) (see also APPENDIX). Computations were performed without interpolation or data smoothing. Glucose concentrations and tracer-to-tracee (tracer-tracee) ratios are presented to facilitate an assessment of whether modeling would under- or overestimate a treatment effect and for comparison of the present constant tracer approach with a previously published variable tracer approach to estimating Ra (17).

Individual observations are given as means and population sample standard errors of the mean. Significance of difference between population sample means was tested using an unpaired Student’s t-test (n = 7).

RESULTS

Model-independent results. Figure 1 shows the occurrence in arterialized plasma of glucose that originated from intubation into the duodenum and midjejenum and that was traced with D-[13C6]glucose. For the same amount of glucose administered (50 g·90 min⁻¹·70 kg body weight⁻¹), the area under the curve fell (P < 0.05, unpaired t-test) by 57 ± 10% on change of infusion site from the duodenum to the midjejenum.

Model-dependent results. The D-[13C6]glucose infused into the duodenum rapidly appeared in the systemic circulation (Fig. 2). The Ra was very nearly equal to the enteral infusion rates in all seven participants, suggesting that the infusion rate was rate limiting for both glucose absorption and systemic Ra. On termination of the enteral infusion, appearance in the systemic circulation decelerated to a plateau, when 98 ± 2% of the...
administered glucose appeared to have passed systematically. The results with all individuals were very similar.

Infusion of the D-[13C6]glucose into the midjejunum gave different results (Fig. 3). Systemic appearance was always less than the infusion rate. Ra values differed substantially between individuals, as did the level of the eventual plateau that signaled a cessation of appearance in the systemic circulation. Cessation of the infusion was not followed by an immediate fall in systemic appearance rate, and the time at which the plateau began tended to be inversely related to the initial Ra of the administered glucose. By contrast with the intraduodenal infusion, in which most glucose passed into the systemic circulation, a mean of only 35 ± 9% of midjejunally administered glucose passed systematically, and the remainder was retained in the intestinal lumen or sequestered by the liver during first pass through this organ.

The average fall in the (model-dependent) systemic glucose appearance on change of infusion site from the duodenum to the midjejunum was 65 ± 9%, similar to the average fall in (model-independent) systemic occurrence of glucose (57 ± 10%).

Not only was the systemic appearance after midjejunal infusion substantially lower than after the duodenal infusion, but it varied with the length of enteral tube that was passed (Fig. 4). The fall in systemic appearance, assessed by regression analysis, was 69 ± 8%/m, which was highly significant (t = 8.7, P = 0.000002).

Tracee concentrations and tracer-tracee ratios. The model we used to estimate the Ra of exogenous glucose after 50 g of oral glucose was found to be accurate (±5% of glucose ingested) compared with a two-compartment reality (9), and errors no greater than this are expected for the present data (Figs. 2–4), because the amounts of glucose administered were similar. Reasons for such small errors are given in Appendix. Rates of systemic appearance of exogenous glucose from the gut are difference estimates from two sets of data modeling, one for nontracer total glucose and one for endogenous glucose; thus enteral Ra is equal to the nontracer total Ra minus the endogenous Ra. Onset of enteral glucose at both sites in the gut decreased the occurrence of endogenous glucose and elevated the tracer-tracee ratio used in calculations of endogenous glucose Ra values (Fig. 5). This suggests that modeling error would tend to overestimate rather than underestimate the endogenous glucose Ra values, which in turn would result in an underestimation (not overestimation) of the systemic Ra values of enteral glucose. By contrast, onset of enteral glucose infusion at both sites was accompanied by a rise in the nontracer total glucose concentration and a fall in the tracer-tracee ratio used in calculation of nontracer total glucose Ra values (Fig. 6). This suggests overall underestimation (rather than overestimation) of both nontracer total glucose and enteral glucose Ra values. Thus differences between the model system used to make rate estimates and the real system caused the two sets of data modeling to introduce potential errors with the same sign, which add to underestimate the systemic appearance of enteral glucose. The tracer-tracee ratios did not change monotonically; this suggests that the errors would be balanced during return toward the initial steady-state tracer-tracee ratios, but by the end of the study the estimate of glucose appearance (Figs. 2–4) would remain an underestimate. Variation in tracer-tracee ratios after duodenal infusions was greater than after midjejunal infusions (Figs. 5 and 6), which suggests that the difference observed in treatment on account of differences between the model and the real system would be underestimated rather than overestimated.
We show for the first time that glucose delivered into the midjejunum of healthy adult humans is very slowly and incompletely transferred to the systemic circulation, whereas there is rapid and nearly complete transfer of glucose administered intraduodenally. Our definition of a midjejunal site requires more precise definition. It was 1 m beyond the pylorus. This accords with the duodenum being the first 25 cm and the jejunum being the next 2 m of small intestine in a total length in vivo of 3–4.5 m (6). Subsequent studies in two of our volunteers showed them to have 3-m-long small intestines in vivo when measured by intubation and fluoroscopy. These lengths contrast with the generalization that the small intestine is 6 m long, which is probably so only after muscular tone is lost postmortem.

The rate and extent of glucose appearance systemically depend on the rate of glucose absorption less the rate at which glucose enters the liver during its first pass through this organ while in blood on its way from the gut to the systemic circulation. The 98 ± 2% (n = 7) systemic appearance of intraduodenally infused glucose is consistent with our previous finding of 97 ± 3% (n = 22) appearance of 50 g oral glucose/70 kg body weight, and the remainder is not significantly different from a 2–8% first-pass sequestration of glucose by the liver (3, 11, 12). As discussed before (9), the accumulation of recently absorbed oral glucose in the liver appears to be largely dependent on the subsequent 40 or so repasses during the course of the absorptive period.

Consideration needs to be given to the question of how glucose becomes retained in the liver as glycogen. Magnetic resonance spectroscopy (MRS) studies show that considerable accumulation of glucose in the liver occurs after oral carbohydrate ingestion, some 20% of the carbohydrate of the meal (17). The present and previous stable isotope data and some previous radiisotope and arteriovenous difference data (see Ref. 9) suggest that probably no more than 5% enters directly after oral and duodenal glucose. Most of the absorbed glucose seems to be available to muscle, where it may be stored as glycogen, with the liver accumulating glucose also from the systemic pool to reach the 20% or more deposited in the liver after a meal (17). This may have important implications for the way we think about regulation of the distribution of glucose between liver and muscle stores.

A possibility exists that, after a meal, more of the carbohydrate reaches the midjejunum with a higher proportion being sequestered by the liver, which may explain both the lower systemic appearance of distally infused glucose (Figs. 3 and 4) and the higher (>5%) accumulation of glucose as liver glycogen after a high-carbohydrate meal (17). Unfortunately, MRS studies would not resolve the question of what proportion of
glucose from the gut enters the liver directly compared with indirectly after passage via the hepatic and systemic circulation. However, MRS studies would enable a distinction to be made between accumulation in the liver of substantial amounts of glucose from the distal intestine and retention within the intestinal lumen; such a distinction merits investigation.

The systemic appearance of midjejunally infused glucose was far from complete, either because of incomplete absorption or because the first-pass hepatic glucose sequestration was substantial, or both. An increase in hepatic glucose sequestration with increasing distance along the small intestine would have important implications for the understanding and potential control of blood glucose concentrations during the absorptive period and would require intraluminal glucose-mediated neurohormonal mechanisms to facilitate, for example, hepatic glycogenesis. To our knowledge there are no candidate mechanisms. We do not believe hepatic glucose sequestration alone can account for all the glucose that failed to reach the systemic circulation. If it is assumed that all the intrajejunal infused glucose was absorbed and that the liver was responsible for the nonappearance systemically, the first-pass hepatic sequestration would have been, on average, 65 ± 8% of each pass. Such an extraction rate would likely also apply to glucose entering the liver from the systemic circulation. At a blood flow rate of 1 l/min through liver, an approximate basal value, a 65% extraction rate, would have completely drained the free glucose from the systemic pool, which could not and did not happen. It follows that incomplete absorption accounts for at least a part of the nonsystemic appearance of the intrajejunal glucose. Should incomplete absorption explain most of the low systemic appearance, the glucose absorption capacity in healthy humans would vary markedly along the length of the first 120 cm of the small intestinal tract, probably due to changes in the density of glucose transporters, as observed in animal studies (2, 4).

A note is warranted about the accuracy of the present methodology to allay certain misconceptions before a conclusion can finally be drawn. It is well established that one-compartment modeling of single isotope-monitored glucose metabolism leads to negative estimates of hepatic glucose production when exogenous (intravenous) glucose infusion rates are known (8). It should not be thought that the dual-isotope approach as used at present has the same result. Modeling using the dual-isotope approach after oral glucose tends to overestimate endogenous (hepatic) glucose production (9, 10) for reasons explained in APPENDIX. Thus the two experimental paradigms should not be confused.

The dual-isotope approach appears particularly good for estimating endogenous (hepatic) glucose production in the present experimental paradigm, provided the glucose distribution volume used is close to total, V_T, as demonstrated in practice (9) and with theory (APPENDIX), but is in substantial error when a fractional or partial V_T (pV_T) is used, where fraction (p) = 0.65 as shown in practice (11) and with theory (1, 10). It is of some concern that such errors are evident in the majority of studies on the systemic appearance of oral glucose (see review in Ref. 9). The explanation for the present result having adequate accuracy is that a multicompartment reality collapses into a single compartment with a volume equal to V_T when glucose concentrations and tracer-tracee ratios change reasonably slowly (APPENDIX). Expressed differently, volume and structure errors (e_v and e_s, respectively), as defined by Cobelli et al. (1), finally balance at zero in such a collapsed reality (APPENDIX). Lowering of the volume to below V_T, such as when pV_T is used, only makes the balance of structure and volume errors worse (by ignoring the second compartment), leading to underestimation of exogenous glucose production.

For comparison of present with previous tracer-tracee ratios, Taylor et al. (17) used a variable tracer infusion to stabilize the ratio for endogenous glucose with residual fluctuation within a twofold range (75–150% basal), whereas in the present study, with a constant isotope infusion, the range of means was not more than threefold (100–300% basal). It is noteworthy that, at any particular glucose concentration, the percentage rise in this ratio has less impact on the result than a percentage fall [a consequence of the term 1 – (a_2/a_1) when a_2 is delayed a_1; see Eq. A6b in APPENDIX]. Although this ratio seems to change markedly in the present study, it is not that much more variable than is achievable with a variable infusion, and we must consider that the changes found extend throughout the pool volume of 230 ml/kg body wt. Keeping this tracer-tracee ratio low is particularly difficult, because endogenous glucose concentrations fall toward zero, so the ratio could easily reach infinity. Nevertheless, rises in this ratio on this account have only small impact on error, because at zero concentration, errors are also zero (see APPENDIX). Estimates of glucose R_a from the gut in the present paradigm are not as good as those estimated for endogenous glucose production (9). Nevertheless, in the present study, as in others (9), we expect accuracy of exogenous glucose production to be within ±5% of the total exogenous glucose load (at any given time and given <50 g intake) compared with a twocompartment reality (10, 11). In other circumstances, greater errors are known and many varied attempts have been made at error minimization (see APPENDIX). Furthermore, the rise to plateau and end point of our endogenous glucose appearance estimates after duodenal glucose were close to expectations (95%) on the basis of arteriovenous difference studies (3, 11, 12), which adds validity to our findings. The limit would of course be 100%, which gives little scope for error in the present and previous (9) data because of the model’s underestimation of systemic appearance of exogenous glucose (as “real” values would then be impossibly >100%).

A further potential misconception is that dilution of tracer and tracee in the portal vein by exogenous glucose will lead to errors in R_a, which does not happen for systemic R_a but does for whole body R_a (and disappearance rate). The difference is due to the rate of
first-pass hepatic glucose sequestration from the gut (as noted in Appendix).

We conclude that the methodology used for estimating the systemic appearance of exogenous glucose is reasonably robust, giving after duodenal glucose infusion an Ra and end point close to but less than the reasonably robust, giving after duodenal glucose infusing the systemic appearance of exogenous glucose is an invariant effective pool volume (VS, as shown in example, an invariant effective pool volume (VS, as shown in arteriovenous difference studies. A substantial fall in intestine in considerable amounts.

APPENDIX

Approaches to error minimization. The real metabolic system is complex, and, by definition, models only approximate the complexity. Differences between real and model systems result in real errors that may be time variant [e(t)]. Since Steele (15) introduced the one-compartment model (Eq. A1a) to estimate a time-dependent glucose Ra [R(t)], at least five approaches have been used to minimize these errors.

\[ R(t) = \frac{R^*(t)}{a(t)} - \frac{V_C(t)\dot{a}}{a} \]  

First, effective parameter estimates have been used. For example, an invariant effective pool volume (VS, as shown in Eq. A1a) is a fraction (p) of the original total glucose distribution volume (VT) such that VS = pVT in Steele's one-compartment model and, importantly, wherein the size of VS depends on the experimental paradigm. Second, a time-variable VS (or p) has been used in place of VT (or pVT) in the one-compartment model to eliminate apparent time dependency (5). Third, more complex models have been introduced with invariant volumes (10, 14, 16). Fourth, experimental design has been changed (by use of variable tracer infusions) to stabilize the tracer-tracee ratio [a(t)] and its derivative (a) (8, 17), and so to make the Ra estimates independent of model structure and volumes (and by extrapolation, independent of the structure of the real system) (7). Fifth, both variable tracer infusions and more complex models have been used (8, 17). The fifth arises because tracer-tracee ratios are impossible to stabilize exactly, and so Ra estimates are always model dependent and yield real errors. In all cases, the Ra estimates have real errors, which by definition cannot be quantified exactly, but upper bounds to the size of the error can be estimated (10, 11), and, short of this, the direction of the error can be elucidated to uncover whether a treatment effect is under- or overestimated because of differences in real errors between treatments.

Multicompartment reality. In the constant tracer infusion dual-isotope paradigm, three rate estimates are possible: rate estimates for endogenous, exogenous, and total glucose. All three rates differ and can have time-dependent real errors of differing size and direction, even when they are applied to the same model. Such errors arise from oversimplification of the multicompartment reality. The most general multicompartment reality is describable in modeling terms, as was done by Cobelli et al. (1) by Eq. A2

\[ R_{a}(t) = R_{a}(t) + R_{1}(t) + R_{2}(t) + \ldots + R_{n}(t) \]  

\[ R_{0}(t) = \frac{R^*(t)}{a(t)} \]  

\[ R_{1}(t) = -\frac{V_C(t)}{a(t)} \cdot \dot{a} \]  

\[ R_{2}(t) = -\left[ 1 - \frac{a(t)}{a_1(t)} \right] \cdot k_{21} \cdot C_2(t) \cdot V_2 \]  

\[ R_{n}(t) = -\left[ 1 - \frac{a(t)}{a_n(t)} \right] \cdot k_{n} \cdot C_n(t) \cdot V_n \]  

Ra(t) is the non-steady-state term that describes the Ra when the tracer-tracee ratio, a, is constant or, as usually happens in practice, changes very slowly. When a changes more than this but not rapidly, a term including the derivative da/dt = \dot{a} is required to retain accuracy, as in R1(t) (Eq. A2c), and so Ra(t) + R1(t) describes the one-compartment model in the nonsteady state, but only when changes in a are not rapid and when V1 approaches VT (as will be described). The sum R0 + R1 appears invalid when the tracer-tracee ratio a changes rapidly, revealing that the real system is at least better described by a two-compartment model in which R0(t) = R0(t) + R1(t) + R2(t), and the tracer-tracee ratio is a1 and a2 in compartments 1 and 2, respectively, and k21, V2, and C2 are the rate parameters from compartment 2 to compartment 1, the volume of compartment 2, and the concentration of tracee in compartment 2, respectively. Noncompartmental analysis reveals that three kinetics may still better maintain accuracy should a change very rapidly. Addition of a third or more nth compartment (also connected to the first) requires addition of an nth term that is identical in structure to term R2(t) for compartment 2, and so the nature and direction of the real error through omitting the nth compartment in the model are the same as for omitting compartment 2. As will be described, the sizes of V1, V2, and C2 are model dependent. For the one-, two-, and three-compartment models, respectively, V1 = Vr, V1 + V2 = Vr, and V1 + V2 + V3 = Vr. The approximations (=) arise because volume estimates are obtained by noncompartmental analysis simultaneously with estimates of the rate parameters (k), such that errors in the determination of V should be balanced by errors in the determination of k.

Collapsing the multicompartment reality into a one-compartment model. Users of one-compartment modeling almost invariably use a glucose distribution volume VS less than VT. It is of interest, therefore, to show whether this affects the ability of the one-compartment model to represent a multicompartment reality. A difficulty with multicompartment models is that only compartment 1 is accessible. Nevertheless, this may be overcome with complicated mathematics. As shown by Madi (10), R2(t) (Eq. A2d) is given by convolution integrals

\[ R_2(t) = -V_2 \cdot \frac{1}{a(t)} \int_{0}^{t} k_{22} e^{-k_{22}(t-\tau)} g(\tau) \cdot \dot{a}_1(\tau) \, d\tau \]  

\[ g(t) = \int_{0}^{t} k_{22} e^{-k_{22}(t-\tau)} C_2(\tau) \, d\tau \]  

As also noted by Madi (10), when C2(t) and \dot{a} change slowly, g(t), an estimate of C2(t), approximately equals C2(t), and the
result of the integral in Eq. A3a approximately equals $C_1(t)\dot{a}_1$, and so Eq. A3a collapses into Eq. A4a

$$R_2(t) = -\frac{V_2 C_1(t)}{a_1(t)} \cdot \dot{a}_1(t) \quad \text{(A4a)}$$

It follows, therefore, that in a two-compartment reality when $C_1(t)$ and $\dot{a}_1$ change slowly, the sum $R_2(t) = R_1(t) + R_2(t)$ is given by the sum of results from Eqs. A2b, A2c, and A4a. In this sum, the last two terms, $R_1(t) + R_2(t)$, simplify to Eq. A5a, which has the same form as in the one-compartment model but in which the volume term is greater because $V_1$ is replaced by $V_1 + V_2$.

$$R_1(t) + R_2(t) = \frac{(V_1 + V_2) C_1(t)}{a_1(t)} \cdot \dot{a}_1(t) \quad \text{(A5a)}$$

The arguments applied here to the second compartment would apply equally to the $n$th compartment, and so, provided $C_1(t)$ and $\dot{a}_1$ change sufficiently slowly, the multicompartment reality can be represented by a one-compartment model (and if $C_1(t)$ and $\dot{a}_1$ do not change at all or change very slowly, a zero compartmental analysis is sufficient, as in Eq. A2b, R0). Demonstration of the adequacy of the one-compartment approach under these circumstances is the nearly identical result for the one- and two-compartment models for both endogenous and exogenous glucose $R_a$ values when, in the one-compartment model, the glucose distribution volume used was $V_1 + V_2$ and when the source of exogenous glucose was 50 g glucose/70 kg body weight and when the tracer infusion was constant, as opposed to variable (9). When $V_1$ alone is used in the one-compartment model, estimates of endogenous glucose appearance are too high, and estimates of both total and exogenous glucose appearance are too low, as was demonstrated under essentially identical conditions by Mari et al. (11). The similarity in $R_a$ estimates with the two-compartment model and the one-compartment model with $V_T = V_1 + V_2$ for the two compartments is evidence of a relatively low rate of change in both $C_1(t)$ and $\dot{a}_1$. The absorption of 50 g glucose/70 kg body weight, as in the present study, evidently perturbs $C_1(t)$ and $\dot{a}_1$ relatively slowly in the context of compartmental modeling, at least in healthy people.

Balance of volume and structure errors in a collapsed multicompartment reality. Real errors $e(t)$ for a one-compartment model have been defined by Cobelli et al. (1) by assuming that a two-compartment model accurately describes the real system, which may be represented as

$$e(t) = e(t) + e_v(t) \quad \text{(A6a)}$$

$$e_v(t) = \left[1 - \frac{a_1(t)}{a_1(t)}\right] \cdot k_{21}(t) \cdot C_2(t) - V_2 \quad \text{(A6b)}$$

$$e_v(t) = -\frac{(V_1 - V_2)}{a_1(t)} \cdot C_1(t) \cdot \dot{a}_1(t) \quad \text{(A6c)}$$

Equation A6b, resulting in $e_v(t)$, is identical to Eq. A2c, resulting in $R_2(t)$ [i.e., $e_v(t) = R_2(t)$]; hence, when $C_1(t)$ and $\dot{a}_1$ change slowly, the structure error collapses, as did $R_2(t)$ from Eq. 3, a and b, to Eq. 4a, to give Eq. A7a

$$e_v(t) = \frac{V_1 C_1(t)}{a_1(t)} \cdot \dot{a}_1(t) \quad \text{(A7a)}$$

When $V_2$ is chosen to be $V_1$, and $V_T = V_1 + V_2$, it follows that $V_3 = V_1$, in Eq. A6c is equal to $V_2$, and so the equations for $e_v(t)$ and $e_v(t)$ become equal but of opposite sign. Thus when $V_5 = V_T = V_1 + V_2$, $C_1(t)$ and $\dot{a}_1$ change slowly, $e_v(t) \approx e_v(t)$ and $e_v(t)$ is approximately zero.

The same arguments apply for the $n$th compartment, provided that $V_1 + V_2 + V_n = V_T$. It follows that when $C_1(t)$ and $\dot{a}_1$ change slowly, as in the present experimental paradigm, a one-compartment model that uses a volume unequal to $V_T$, such as when it is $nV_T$, results in a modeling error, of which there are many examples in the literature.

Mistransposition of the experimental paradigm. It must not be thought that the present study result would suffer from errors causing negative estimates of endogenous or hepatic glucose production, and hence overestimation of exogenous glucose appearance. It has been hypothesized that estimates of endogenous glucose production can be derived as the difference in total glucose $R_a$ calculated using a constant tracer infusion, a one-compartment model, and known rates of unlabeled exogenous glucose infusion, as in the early hot euglycemic clamp. In this experimental paradigm, it is known that 1) the overall error is large, 2) the direction of the error causes endogenous glucose production to be underestimated [the so-called “negative hepatic glucose production problem” (5, 8)], and 3) the size of the error can be reduced (but not to zero) by choosing a glucose distribution space much below the total glucose distribution volume in the body. The error in endogenous glucose production estimates in this experimental paradigm is sufficiently large to necessitate variable tracer infusion to minimize the error. By contrast, in the present dual-isotope paradigm, the endogenous glucose production (1) is in small error (see Ref. 9 and above), 2) when in error, is overestimated, and 3) can be obtained using one-compartment analysis and effective glucose distribution volume near to the total glucose distribution volume; forcing a lower volume would force the introduction of an imbalance of structure and volume errors. Furthermore, in the first of these two experimental paradigms, wherein a negative hepatic glucose production problem has been identified, a variable tracer infusion would be needed to minimize variation in the tracer-to-total glucose ratio specifically, because it is total glucose appearance that is estimated by modeling. By contrast, in the second, and presently used, experimental paradigm, the endogenous (not total) glucose production rate is estimated directly, and the variable tracer infusion, when needed, would be to minimize the tracer to an endogenous (not total) glucose ratio (9). This has implications for the error estimates, for when total glucose appearance is estimated, it may be associated with a rising $C_1$ that, according to Eqs. A6b and A6c, would magnify the error balance $e(t)$. By contrast, when endogenous glucose appearance is estimated, it is subject to a falling $C_1$, which would diminish the error.

When estimates of $R_a$ and glucose disposal rate are not whole body estimates, when exogenous glucose is administered intravenously, the estimates of $R_a$ are whole body estimates; however, this is not the case when exogenous glucose is administered via the oral or enteral route. Then $R_a$, obtained by either one- or multicompartment models, is for rates of entry into the systemic glucose pool, which differs from the whole body glucose $R_a$ in a significant way. Thus the gut and liver have to be viewed as a single unit from which glucose appears, both endogenous and exogenous. With such models, the estimate of systemic $R_a$ is less than whole body $R_a$ by the rate of hepatic sequestration of glucose that is derived directly from the gut. It might be thought that dilution of tracer by unlabeled exogenous glucose in the portal vein would interfere with making accurate $R_a$ estimates. However, provided gut-derived glucose dilutes the tracer and tracee from the systemic circulation equally, the principle of equivalent tracer supply is upheld. It is worthy of note, however,
that estimates of glucose disposal rates, should they be made, will also not represent whole body rates, as these will be underestimated by the rate of first-pass hepatic glucose sequestration.

We thank the Ministry of Agriculture, Fisheries, and Food for financial support and the Biotechnology and Biological Sciences Research Council for the provision of facilities.

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Received 21 July 1997; accepted in final form 23 June 1998.

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