

Pentose pathway in human liver

(carbohydrate metabolism/ribose/glucose/glucuronides)

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ABSTRACT [1-¹⁴C]Ribose and [2-¹⁴C]glucose were given to normal subjects along with glucose loads (1 g per kg of body weight) after administration of diflunisal and acetaminophen, drugs that are excreted in urine as glucuronides. Distributions of ¹⁴C were determined in the carbons of the excreted glucuronides and in the glucose from blood samples drawn from hepatic veins before and after glucagon administration. Eighty percent or more of the ¹⁴C from [1-¹⁴C]ribose incorporated into the glucuronic acid moiety of the glucuronides was in carbons 1 and 3, with less than 8% in carbon 2. In glucuronic acid from glucuronide excreted when [2-¹⁴C]glucose was given, 3.5–8.1% of the ¹⁴C was in carbon 1, 2.5–4.3% in carbon 3, and more than 70% in carbon 2. These distributions are in accord with the glucuronides sampling the glucose unit of the glucose 6-phosphate pool that is a component of the pentose pathway and is intermediate in glycogen formation. It is concluded that the glucuronic acid conjugates of the drugs can serve as a noninvasive means of sampling hepatic glucose 6-phosphate. In human liver, as in animal liver, the classical pentose pathway functions, not the L-type pathway, and only a small percentage of the glucose is metabolized via the pathway.

The reactions comprising the pentose pathway were defined many years ago (1, 2). This pathway functions in many tissues (3, 4) and as a cycle (2). In its oxidative portion glucose 6-phosphate (glucose 6-P) is oxidized to pentose 5-P and CO₂. In its nonoxidative portion pentose 5-P forms glucose 6-P and glyceraldehyde 3-P. In this conversion carbon 1 of the pentose 5-P becomes carbons 1 and 3 of the glucose 6-P.

Quantitative contributions of the pathway to glucose metabolism *in vivo* and *in vitro* have been estimated from the incorporations of ¹⁴C from [2-¹⁴C]glucose into carbons 1 and 3 relative to that in carbon 2 of glucose 6-P (2, 3). Since, in the conversion of glucose 6-P to glycogen, there is no randomization of carbon, glucose from glycogen has been used as the measure of the distribution of ¹⁴C in the glucose 6-P. Use of this approach for estimating the pathway's contribution in human liver *in vivo* has not been possible, because of the inordinate amount of label that would have to be administered due to the limited amount of liver that can be reasonably removed to isolate glycogen or glucose 6-P.

Since the glucuronides of diflunisal, an aspirin-like compound, and acetaminophen are formed in liver, and UDP-glucuronate is formed from glucose 6-P, these glucuronides sample the glucose unit of the glucose 6-P pool from which they are formed. This offers the opportunity to sample in quantity, noninvasively, that pool of glucose 6-P. We (5) have provided evidence that the UDP-glucuronate and the glucose units of glycogen are derived from the same pool of hepatic glucose 6-P. We now report the distributions of ¹⁴C in the glucuronides excreted by humans who had been given

diflunisal and acetaminophen with [1-¹⁴C] ribose and [2-¹⁴C]glucose. This work was done to establish the functioning of the pentose pathway and quantify its contribution to glucose utilization in human liver.

METHODS

Subjects. The subjects were healthy volunteers, six men and three women, aged 25–38, weighing 56–81 kg and each within 15% of ideal body weight. Each consumed a weight-maintaining diet containing at least 200 g of carbohydrate for at least 3 days before the study. None were taking any medication. The experimental protocol was approved by the Human Investigation Committees at Huddinge University Hospital and University Hospitals of Cleveland. Informed consent was obtained from each subject.

Procedure. The subject ingested at zero time, after an overnight fast, within a 5-min period, 1 g of glucose per kg of body weight, in a 30–46% (wt/vol) aqueous solution. A trace amount of [2-¹⁴C]glucose, 20 or 40 μCi (1 μCi = 37 kBq), was added to the glucose ingested by each of five of the subjects and 40 mg of [1-¹⁴C]ribose, 40 μCi, was added to the glucose ingested by one subject. Into each of the three other subjects, 40 mg of [1-¹⁴C]ribose, 20 or 40 μCi, in isotonic saline was infused through a peripheral vein at the rate of 12 ml/hr for 3 hr beginning at the time of glucose ingestion. Two of the subjects, one given [2-¹⁴C]glucose and the other [1-¹⁴C]ribose, each ingested 1 g of diflunisal 30 min before ingesting the glucose. Three of the subjects given labeled glucose, and two of those given labeled ribose, each ingested 1.5 g of acetaminophen 30 min to 1 hr before ingesting the glucose. The other two subjects took no drug. Each subject ingested hourly about 250 ml of water. A no. 7 or 8 Courmand catheter was introduced into a hepatic vein of each of seven of the subjects just before he or she ingested glucose or shortly before 3 hr after the ingestion, except for one subject in whom the catheter was introduced 4½ hr after ingestion. Glucagon was infused at 3 hr, except in the one subject at 4½ hr, through a peripheral vein at the rate of 36 ng per kg of body weight per min (6). Fifty milliliters of blood was drawn at 3 hr from a peripheral vein of each of the two subjects not given glucagon and from the hepatic veins of the seven subjects just before they were given glucagon and at 15 and 30 min into its infusion. Blood glucose concentrations were determined before glucose ingestion and every 30 min thereafter through the 3-hr period, or in one case 4½-hr period, and then every 5 min during the 30 min of glucagon infusion. Urine was collected after glucose ingestion in two time periods, 0–1½ hr and 1½–3 hr.

Materials. D-[2-¹⁴C]Glucose and D-[1-¹⁴C]ribose were purchased from New England Nuclear. Evidence of their purity, beyond that provided by the manufacturer, was the demon-

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stration that each gave a single peak of radioactivity with the mobility of the sugar on high-pressure liquid chromatography (HPLC) on an Aminex HPX 87P carbohydrate-analysis column (Bio-Rad) with water at 80°C as solvent (7). A sample of the [2-¹⁴C]glucose was degraded as described below. The percent distribution of ¹⁴C found in its carbons was C-1, 0.0; C-2, 96.7; C-3, 0.5; C-4, 1.1; C-5, 0.6; C-6, 1.1; the recovery of ¹⁴C was 96.3%. On degradation of unlabeled glucose in the presence of a trace of the [1-¹⁴C]ribose, 96.3% of the ¹⁴C was recovered in carbon 2 of the glucose. This is evidence beyond that provided by the manufacturer for the ¹⁴C in the ¹⁴C-labeled ribose being localized to carbon 1. Diflunisal (Dolobid) in 500-mg tablets was a gift of Merck Sharp & Dohme. Acetaminophen (Alvedon) in 500-mg tablets was purchased from Astra Pharmaceutical (Södertälje, Sweden).

Analyses. Glucose concentration in blood plasma was determined enzymatically (8). Glucose was isolated from blood as described (5). In brief, perchloric acid was added to each 50-ml blood sample. The precipitate was removed by centrifugation, the supernatant was neutralized with KOH, and potassium perchlorate was removed by centrifugation. The supernatant was deionized by the use of a mixed-bed ion-exchange resin, and the glucose in the resulting solution was isolated by the use of preparative paper chromatography and then the HPLC system.

Each urine sample was adjusted to pH 4.5. The amount of glucuronide in each was determined (9, 10). Less glucuronide, usually about one-fourth to one-fifth as much, was in the 0- to 1½-hr collection as in the 1½- to 3-hr collection (11). The two collections from each subject were combined, except for three subjects, each given acetaminophen, where there was sufficient glucuronide in the 0- to 1½-hr collection for separate analyses. Although more acetaminophen glucuronide than diflunisal glucuronide was excreted in the 3-hr period (11, 12), giving a greater yield of ¹⁴C in the acetaminophen glucuronide, the isolation of the acetaminophen glucuronide, because of its greater solubility in water, proved more tedious than that of the diflunisal glucuronide.

The diflunisal glucuronide-containing urine samples were treated as described (5). In brief, the glucuronide in the urine was continuously extracted into ether and reduced with diborane to its glucoside. The glucoside was hydrolyzed with β-glucosidase, and glucose from the reaction mixture was isolated by the preparative paper chromatographic and HPLC systems.

The yield of acetaminophen glucuronide in the 3-hr urine collections ranged from 170 to 369 mg. Each acetaminophen glucuronide-containing urine was lyophilized to about 1/10th its volume and then reconstituted to its original volume with

methanol. About 10 g of anhydrous sodium sulfate was added, and the precipitate that formed was removed by filtration. The filtrate was evaporated to about 1/15th the original urine volume. This concentrate was reconstituted with acetone to the original urine volume. The precipitate that formed contained the glucuronide. It was collected by filtration and dissolved in water. The aqueous solution was made pH 8 with NaOH and applied to an ion-exchange resin, AG 1-X8 (Bio-Rad), in its acetate form. The column was washed with water and then with increasing concentrations of acetic acid to 5 M (13, 14). The fractions in which the glucuronide eluted were identified by using carbazole (15). These fractions were combined and evaporated to dryness, the residue was dissolved in a minimal amount of methanol, and the glucuronide was reduced with diborane to its glucoside. The acetaminophen glucoside was treated in the same manner as the diflunisal glucoside; i.e., it was hydrolyzed with β-glucosidase and the glucose was isolated by the paper chromatographic and HPLC systems. The overall yield of glucose from the urinary acetaminophen glucuronide averaged 43% of the theoretical yield.

Each glucose sample from blood and urine was degraded to yield each of its carbons as CO₂. Each CO₂ sample was assayed for ¹⁴C, as detailed (5). Each glucose sample degraded had at least 1600 dpm in its six carbons, and all but two of the glucose samples degraded had more than 2600 dpm.

RESULTS

Eighty percent or more of the ¹⁴C was in carbons 1 and 3 of the glucose from the blood and urinary glucuronides of the four subjects given [1-¹⁴C]ribose (Table 1). Except for glucose from the blood of subject GD, there was 2–5 times as much ¹⁴C in carbon 3 as in carbon 1. Incorporation was somewhat more into carbon 1 than into carbon 3 of glucose from the blood of subject GD collected at 1 hr after [1-¹⁴C]ribose ingestion, and was somewhat less in the blood collected at 3 hr. It was still less after glucagon administration, at which time there was about four-fifths as much ¹⁴C in carbon 1 as in carbon 3. Only 1.3–7.5% of the ¹⁴C was in carbon 2, and small percentages were found in the remaining three carbons. There was no difference in the distributions of ¹⁴C in the glucoses from the urinary glucuronides of the two subjects, GD and LB, whose collections were not combined. For subject LB, distributions in glucose from blood before and after glucagon and from urine were essentially the same. Too little ¹⁴C for degradation was found in the glucose from the glucuronide in the 3-hr urine collection of subject LN.

Seventy percent or more of the ¹⁴C was in carbon 2 of the glucose from the blood and urinary glucuronides of the five

Table 1. Distributions of ¹⁴C in glucose from blood before and after infusion of glucagon at 3 hr and from urinary glucuronides of subjects given [1-¹⁴C]ribose i.v. or orally

Subject	Mode	Drug	Source of glucose	% of ¹⁴ C in carbon						Recovery, %
				C-1	C-2	C-3	C-4	C-5	C-6	
HN	i.v.	None	Blood, 3 hr	18.3	4.6	71.3	2.8	1.8	1.2	101.0
			Blood, 3¼ hr	15.5	7.0	73.5	1.5	1.3	1.2	94.5
LN	i.v.	Diflunisal	Blood, 3 hr	26.1	4.6	63.0	2.0	1.8	2.5	91.2
			Blood, 3¼ hr	22.0	7.5	66.4	1.7	1.0	1.4	98.0
GD	p.o.	Acetaminophen	Blood, 1 hr	51.2	1.7	42.2	1.1	0.5	3.3	102.7
			Blood, 3 hr	41.8	3.6	45.0	3.6	2.5	3.5	100.5
			Blood, 3½ hr	36.2	4.3	44.5	4.8	3.1	7.1	104.3
			Urine, 0–1½ hr	28.7	5.5	58.0	2.4	1.8	3.6	127.0
			Urine, 1½–3 hr	28.1	2.8	62.3	1.5	1.7	2.6	104.1
LB	i.v.	Acetaminophen	Blood, 3 hr	27.7	2.5	66.5	1.5	0.8	1.0	98.7
			Blood, 3½ hr	23.4	2.7	67.5	2.9	1.6	1.9	93.4
			Urine, 0–1½ hr	23.8	1.3	72.5	1.1	0.4	0.9	96.6
			Urine, 1½–3 hr	22.3	1.3	72.6	2.6	0.5	0.7	95.8

p.o., *per os*.

Table 2. Distributions of ^{14}C in glucose from blood before and after glucagon administration and from urinary glucuronides of subjects given $[2\text{-}^{14}\text{C}]\text{glucose}$ orally

Subject	Drug	Source of glucose	% of ^{14}C in carbon						Recovery, %
			C-1	C-2	C-3	C-4	C-5	C-6	
MF	None	Blood, 4½ hr	3.6	77.6	2.6	3.7	5.2	7.3	96.7
		Blood, 4¾ hr	5.2	70.0	3.0	6.5	6.1	9.2	97.8
MW	Diflunisal	Blood, 3 hr	0.6	94.9	0.6	0.5	0.6	2.9	96.3
		Blood, 3¾ hr	2.4	89.4	1.6	1.6	2.3	2.7	97.7
		Urine	3.5	86.2	3.0	2.2	2.4	2.6	93.1
GD	Acetaminophen	Blood, 3 hr	1.3	90.7	1.0	1.4	1.2	4.4	105.9
		Urine	8.1	79.3	3.7	1.7	2.6	4.6	98.1
CO	Acetaminophen	Blood, 3 hr	2.1	90.7	1.6	0.8	1.3	3.5	95.4
		Blood, 3½ hr	3.2	89.7	2.2	1.9	2.0	1.0	97.1
		Urine, 0–1½ hr	6.1	74.4	4.3	7.4	4.9	2.6	90.9
		Urine, 1½–3 hr	6.3	83.8	3.6	1.6	1.9	2.8	91.4
HL	Acetaminophen	Blood, 3 hr	2.4	90.6	2.2	1.5	2.5	0.7	94.9
		Urine	4.5	84.1	2.5	3.0	3.5	2.4	95.3

subjects given $[2\text{-}^{14}\text{C}]\text{glucose}$ (Table 2). There was less randomization of ^{14}C in blood glucose before glucagon infusion than during it, and there was more randomization in glucose from glucuronide than in glucose from blood drawn during glucagon infusion. Carbon 1 had 1.2–2 times as much ^{14}C as carbon 3. Thus, in the glucose from the urinary glucuronides, 3.5–8.1% of the ^{14}C was in carbon 1 and 2.5–4.3% in carbon 3. There were also small percentages of ^{14}C in carbons 4, 5, and 6.

Plasma glucose concentrations averaged 95 mg/dl (range, 70–134 mg/dl) just before glucagon infusion and reached concentrations 2.2 times higher (range, 1.6–2.9) during glucagon infusion. Distributions were essentially the same whether diflunisal or acetaminophen was given. While only one subject was given $[1\text{-}^{14}\text{C}]\text{ribose}$ (HN in Table 1) and only one $[2\text{-}^{14}\text{C}]\text{glucose}$ and no drug (MF in Table 2), the distributions in the glucose from their blood were similar to those of the glucose from the subjects given drugs.

DISCUSSION

The distributions of ^{14}C we have found in the glucuronides excreted by humans given $[1\text{-}^{14}\text{C}]\text{ribose}$ and $[2\text{-}^{14}\text{C}]\text{glucose}$ are similar to the distributions found in glycogen and glucose 6-*P* of rat livers perfused with $[1\text{-}^{14}\text{C}]\text{ribose}$ and $[2\text{-}^{14}\text{C}]\text{glucose}$ (16) and in liver glycogen from rats given $[2\text{-}^{14}\text{C}]\text{glucose}$ (3, 4). Distributions of ^{14}C in blood glucose and urinary glucuronides after $[1\text{-}^{14}\text{C}]\text{ribose}$ was given (Table 1) are similar to the distributions in blood glucose found by Hiatt (17) when he gave $[1\text{-}^{14}\text{C}]\text{ribose}$ to a patient. They are also in accord with glucose in the urine from a diabetic subject given $[1\text{-}^{14}\text{C}]\text{ribose}$ having 31% of its ^{14}C in carbon 1 (18).

The glucuronides had 80% or more of their ^{14}C in carbons 1 and 3, in accord with metabolism of the ribose being by the pentose pathway. The small percentage of ^{14}C from $[1\text{-}^{14}\text{C}]\text{ribose}$ in carbon 2 is attributable to recycling of $[1,3\text{-}^{14}\text{C}]\text{glucose 6-}P$ formed in the pathway. Small incorporations into carbon 6 and into carbons 4 and 5 can occur by the formation of $[1,3\text{-}^{14}\text{C}]\text{lactate}$ followed by synthesis of glucose 6-*P* (5). Alternatively, the incorporations may be attributable to transaldolase exchange (19) and/or futile cycling at the fructose 6-*P* \rightleftharpoons fructose 1,6-*P*₂ level (20).

Ribulose 5-*P* is the pentose 5-*P* formed in the oxidative portion of the cycle. In the nonoxidative portion ribulose 5-*P* is epimerized to xylulose 5-*P* and isomerized to ribose 5-*P* (i.e., xylulose 5-*P* \rightleftharpoons ribulose 5-*P* \rightleftharpoons ribose 5-*P*). Carbon 1 of the xylulose 5-*P* is converted to carbon 1 of glucose 6-*P*, and carbon 1 of ribose 5-*P* is converted to carbon 3 of glucose 6-*P*. Thus, with unlabeled ribulose 5-*P* being formed in the oxidative portion from unlabeled glucose, here from the glucose load, and $[1\text{-}^{14}\text{C}]\text{ribose}$, isotopic nonequilibrium of

the pentose 5-phosphates, resulting in higher specific activities of ribose 5-*P* than of xylulose 5-*P*, explains the incorporations into carbon 3 related to those in carbon 1 (17).

Williams *et al.* (21) reported that ^{14}C was incorporated into carbon 2 of glucose 6-*P* when $[1\text{-}^{14}\text{C}]\text{ribose 5-}P$ was incubated for short periods with a rat liver enzyme preparation. Reactions yielding such incorporation, with the oxidative portion of the pentose pathway, comprise the L-type pathway that he and his coworkers proposed (Fig. 1) (22). We believe there is convincing evidence that the L-type pathway does not function in livers of animals (4, 16, 23–25). It also does not function in human liver, as evidenced by the incorporation of ^{14}C from $[1\text{-}^{14}\text{C}]\text{ribose}$ into carbons 1 and 3, but not carbon 2, of glucose and the glucuronides (Table 1).

Incorporations from $[2\text{-}^{14}\text{C}]\text{glucose}$ into carbons 1 and 3 of the glucose (Table 2) are in accord with the randomization of the ^{14}C occurring via the pentose pathway. The distribution of ^{14}C in blood glucose before glucagon administration is the distribution of a mixture of labeled glucose formed from metabolites of $[2\text{-}^{14}\text{C}]\text{glucose}$ and unmetabolized $[2\text{-}^{14}\text{C}]\text{glucose}$. The action of glucagon results in the addition to the blood of glucose from liver glycogen formed from $[2\text{-}^{14}\text{C}]\text{glucose}$ that was metabolized. In contrast, the gluco-

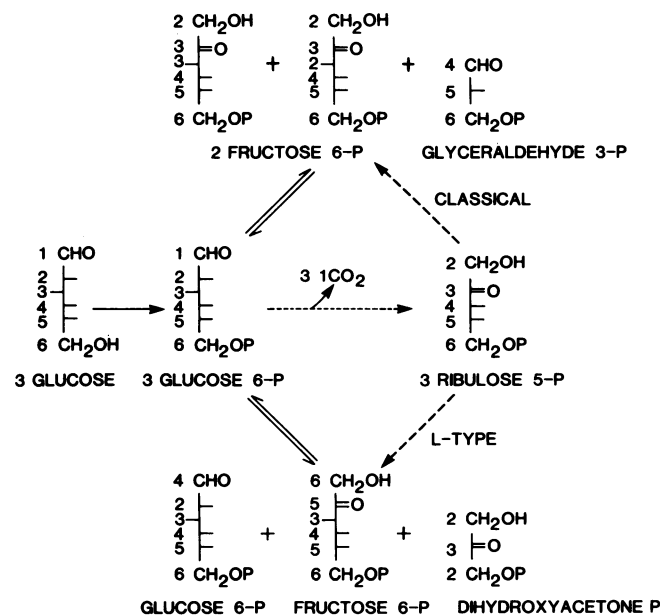


FIG. 1. Rearrangements of the carbons of glucose in the classical pentose and L-type pathways.

ronide reflects only glucose carbons that have entered the metabolic scheme to the level of UDP-glucose. This explains why the randomization of ^{14}C in the glucose from the glucuronide is greater than in the blood glucose and why the randomization in the blood glucose is less before glucagon infusion than during it.

We cannot be certain that isotopic steady state was achieved. Except for subject CO of Table 2, where the distributions at 0–1½ and 1½–3 hr were similar, incorporations from [2- ^{14}C]glucose into glucuronide were too small to allow reliable measurement of the incorporations of ^{14}C from the 0- to 1½-hr collections. Attainment of a steady state for the glucuronide appears to be dependent on the attainment of a steady state of the UDP-glucuronic acid pool, which should be relatively small and rapidly turning over. The rate of urinary excretion of acetaminophen glucuronide is rapid (11, 26, 27), and the biliary route of elimination of acetaminophen seems to be less important in humans than in rats (28).

Similar distributions in glucose from the blood and glucuronide of LB (Table 1) provide further support for glucose, the glucose units of glycogen, and UDP-glucuronate being derived from the same hepatic glucose 6-*P* pool (5). We do not know why the distributions in glucose from the blood and from the urinary glucuronide of GD differ. Ribose was given orally, rather than intravenously. The distribution in the blood after glucagon administration is intermediate between that in blood before glucagon administration and that in the glucuronide. This is in keeping with the glucose from glycogen that was released having a distribution similar to that in the glucuronide.

Pentose-pathway activity is apparently no greater in human liver than in rat liver, since—although lipogenesis is reported to be greater in human liver than in rat liver (29), the [2- ^{14}C]glucose was administered in a glucose load, which should favor lipogenesis, and NADPH is a cofactor required in lipogenesis—the randomizations of ^{14}C from [2- ^{14}C]glucose in the glucuronides are no greater than the distributions in glycogen and glucose 6-*P* from rat liver (3, 4, 16).

Methods are available for estimating the contribution of the pentose pathway by using a model encompassing the pentose and Embden–Meyerhof pathways, the Krebs cycle, and glycogen formation—i.e., circumstances in peripheral tissues (2, 3). For those tissues, the expression $C1/C2 = 2PC/(1 + 2PC)$ can be used to make estimates, where C1 and C2 are the relative incorporations of ^{14}C from [2- ^{14}C]glucose into carbons 1 and 2 of glucose 6-*P* and PC is the fraction of glucose metabolized via the pathway.

A method exists for quantifying the contribution of the pentose pathway to glucose utilization by liver *in vitro* (30), but not *in vivo*. In gluconeogenesis, ^{14}C from [2- ^{14}C]glucose is incorporated via [2- ^{14}C]lactate, or its metabolic equivalent, in about equal amounts into carbons 1 and 2 of glucose 6-*P* (31). No more ^{14}C should be incorporated in carbons 1 and 2 than in carbons 5 and 6, and the ratio of the incorporation into carbon 1 to that into carbon 6 should be the same as the ratio of incorporation into carbon 2 to that into carbon 5.¶ Because of this incorporation into carbons via gluconeogenesis, the above expression can provide only an estimate of the maximum contribution of the pentose cycle to glucose metabolism in liver (i.e., in attributing all the incorporation into carbon 1 to the pentose cycle). Introduction of the percentages of ^{14}C carbons 1 and 2 of the glucuronides into the expression yields an estimate of 2–6% of glucose utilization

being via the pentose pathway.¶ Because the relative contribution of the pentose cycle is so low, a more precise estimate is not possible.

¶Distributions in Table 2 also allow estimates of the maximum contribution to hepatic glucose 6-*P* formation from glucose via the direct pathway relative to the contribution via the indirect pathway (5). The maximum direct-pathway contribution is 74.4–86.2% before correction for the percent incorporations into carbon 2 via gluconeogenesis and the effect of the pentose cycle. These corrections are small, so the distributions indicate a contribution somewhat greater than the 65% estimated from distributions obtained after administration of [6- ^{14}C]glucose (5).

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¶We gave a normal subject, who had fasted overnight, a glucose load with acetaminophen and infused a trace amount of L-[3- ^{14}C]lactate for 3 hr. Glucose from the glucuronide he excreted had the percent distribution C-1, 24.4; C-2, 19.7; C-3, 4.5; C-4, 4.6; C-5, 19.8; C-6, 27.0; recovery was 94%.