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A Difference in the In Vivo Cerebral Production of [1-^{14}C] Lactate From D-[3-^{14}C] Glucose in Chronic Mental Patients

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Data from a study in which 12 chronic mental patients and 12 control subjects were given D-[3-^{14}C] glucose intravenously in our arterio-venous technique for determining cerebral metabolism in vivo were reexamined. Previously unpublished whole-blood lactate determinations in these experiments indicated a cerebral production of much higher specific activity of [1-^{14}C]-lactate from the D-[3-^{14}C] glucose by mental patients. Of several possible explanations offered for this difference, the most likely was that involving a small lactate compartment(s) in some specific region(s) in which decarboxylation of the endogenously formed cerebral lactate was partially inhibited. Two other experiments with mental patients (one given [U-^{14}C] glucose and the other, [1-^{14}C] glucose) whose extraordinary results were described, in part, in a previous report, were interpreted as more extreme examples of the production of higher specific activity ^{14}C-lactate from ^{14}C-glucose by mental patients' brains upon their very unusual whole blood lactate data.

Key words: cerebral metabolism, D-[3-^{14}C] glucose, brain lactate, mental patients

INTRODUCTION

Some unusual results in our recent work on an animal model for the determination of cerebral regional intermediary glucose metabolism in humans in vivo using Positron Emission Transverse Tomography led us to an extensive reexamination of a previous study employing D-[3-^{14}C] glucose as the injected substrate in our arterio-venous technique [Sacks, 1961, 1965a]. In that series of 24 experiments, all were done using D-[3-^{14}C] glucose made by the National Bureau of Standards laboratory [Frush et al, 1965] specifically for our laboratory. The chronic mental patients studied were drug-free for at least 11 months. In addition, in each experiment, six or seven arterio-venous sets of blood samples were assayed for radioactivity of C_1 of lactate and for $C_2 + C_3$ of lactate employing a sensitive procedure developed by our laboratory [Sacks, 1961]. These lactate data, not hitherto reported, form the basis for this article.

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SUBJECTS AND METHODS

All subjects were considered free of metabolic disturbances and were in the post-absorptive state. The mental patients were classified by the staff as chronic schizophrenic patients* and were in the same age group (40–60 years) as the normal subjects. In addition, they had not received any psychopharmacological or shock treatment for a period of at least 11 months preceding the test. Their average period of hospitalization was about 15 years, with a range from 9–34 years.

The method used for the determination of cerebral metabolism in humans was that developed in this laboratory [Sacks, 1969, 1973, 1976]. In it, an intravenous (IV) injection of a labeled substrate (D-[3-^{14}C] glucose, 90 μCi) is given and then simultaneous arterial (femoral) and venous (superior bulb of internal jugular) blood samples are drawn at various time intervals. These blood samples are analyzed for radioactivity of the injected substrate, of the end product of metabolism (carbon dioxide and/or water), and of intermediate metabolites (ie, lactate and pyruvate). The increase in radioactivity of the end product in venous blood over its radioactivity in arterial blood is considered due to catabolism of the substrate by the brain. Carbon dioxide-specific activities and whole blood glucose radioactivities were determined as previously described [Sacks, 1957, 1965a]. However, in this report, the specific activities of glucose taken up by the brain were calculated using arteriovenous (A-V) differences of unlabeled and labeled glucose. This was considered to be a more accurate representation of the ^{14}C-glucose actually used by the brain in the production of ^{14}C-lactate and $^{14}CO_2$ than the venous glucose-specific activity used before.

Whole blood lactic acid was determined following the method of Barker and Summerson [1941]. For the determination of lactate radioactivity, we modified the method of Long [1946] in which lactate is oxidized with ceric sulfate to acetaldehyde and CO_2, as follows [Sacks, 1961]: carrier lactate (10 mg) was added and the acetaldehyde (from C_2 and C_3 of lactate) was collected in a solution of 0.2%, 2,4-dinitrophenylhydrazine in 6 N HCl (instead of being collected in bisulfite), and the resulting precipitate was recrystallized from ethanol. The 2,4-dinitrophenylhydrazones were oxidized to CO_2 which was collected and assayed as before [Sacks, 1956]. The carboxyl carbon (C_1) of lactate was collected as $BaCO_3$ by adding a tube containing $Ba(OH)_2$–$BaCl_2$ solution to the end of the reaction train after first having the intake air pass through ascarite and an NaOH solution to remove CO_2. Using ^{14}C-labeled compounds, it was determined that no contamination was due to the following: glucose, glutamate, glutamine, GABA, aspartate, and alanine. About 39% of ^{14}C-pyruvate could be detected with this method. That this contaminant was not of importance in our determinations of lactate-specific activities was seen in two of the experiments in which whole blood ^{14}C-pyruvate-specific activities were assayed as before [Sacks, 1961].

D-[3-^{14}C] Glucose was prepared using a chemical procedure developed by the laboratory of Dr. H. S. Isbell of the National Bureau of Standards [Frush et al, 1965], with the aid of a grant from the Psychopharmacology Service Center of the National Institutes of Mental Health.

*All mental patients and control subjects were examined by Dr. George Simpson, the staff physician in charge of the research ward of the Rockland Research Institute, to assure accuracy of diagnosis and absence of organic brain disease and of metabolic disturbances.

RESULTS

In Figure 1, we have plotted (semilogarithmically) the specific-activity time curves for glucose taken up by brain and for lactate and CO_2 produced by the brain for control subjects and for chronic mental patients. Specific activity was calculated as percent of injected activity per mg glucose, lactate, or CO_2 carbon. Lactate-specific activities were calculated similarly to glucose and CO_2-specific activities using V-A differences of labeled and unlabeled whole blood lactate, and therefore represent specific activities of lactate produced by brain from the ^{14}C-glucose and added to the venous return blood. With lactate, the data were not as consistent as with CO_2 and glucose in that, in some cases, A-V differences for either labeled or unlabeled (or both) occurred so that no calculations were done in such instances. This was not unexpected, since lactate is both metabolized and produced by the brain in humans in vivo [Sacks, 1976]. Nevertheless, the data resulted mostly in calculations of lactate *produced by brain*, thereby allowing a valid comparison of specific-activity values between mental patients and control subjects. Since no significant ^{14}C was found on C_2 and C_3 of whole blood lactate in these experiments, we feel justified in calling it [1-^{14}C]-lactate. Such labeling would result from the metabolism of [3-^{14}C] glucose by the Embden-Meyerhof-Parnas (EMP) pathway. From Figure 1, it can be seen that brain-produced lactate-specific activities (curves L) were considerably higher after the first few minutes, in comparison to the brain-uptake glucose (precursor)-specific activities (curves G) with mental patients than control subjects.

To compare the relationships of products to precursor, we have plotted the ratios, at various times after injection, of specific activities of brain glucose uptake and of CO_2 and lactate produced (Fig. 2). The ratios of brain-produced lactate to brain-uptake glucose-specific activities varied about the theoretical value of 1 in control subjects, but, with

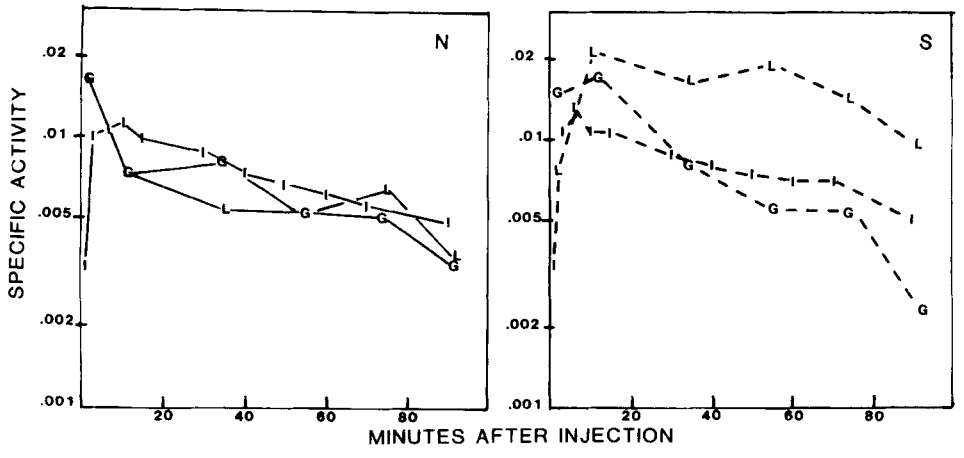

Fig. 1. Average specific-activity time curves (plotted semilogarithmically) for 12 control subjects (solid lines) and 12 chronic mental patients (dotted lines) given D-[3-^{14}C] glucose IV. Curves G represent specific activity of [3-^{14}C] glucose taken up by brain. Curves I and L represent specific activity of $^{14}CO_2$ and ^{14}C-lactate produced by brain, respectively. Specific activity calculated as percent of injected activity per mg glucose, lactate, or CO_2 carbon.

chronic mental patients, they started at about 0.5 and rose rapidly to about 4. Ratios of lactate to CO_2 (both products of glucose metabolism)-specific activities for control subjects started at about 2.5 and then varied about a value of 1; whereas, with chronic mental patients, the ratios started at about 1 and rose to about 2.5. In contrast, the ratios of brain-produced CO_2 to brain-uptake glucose-specific activities showed similar values for both groups.

DISCUSSION

The data presented indicate that the [1-^{14}C]-lactate produced from [3-^{14}C]-glucose by the schizophrenic brain and added to the venous blood had considerably higher specific activity (after the first few minutes following a single injection of D-[3-^{14}C]-glucose) than did that of the control subject. Several possible explanations could be offered for this difference. First, there may have been a difference in the uptake and metabolism of the

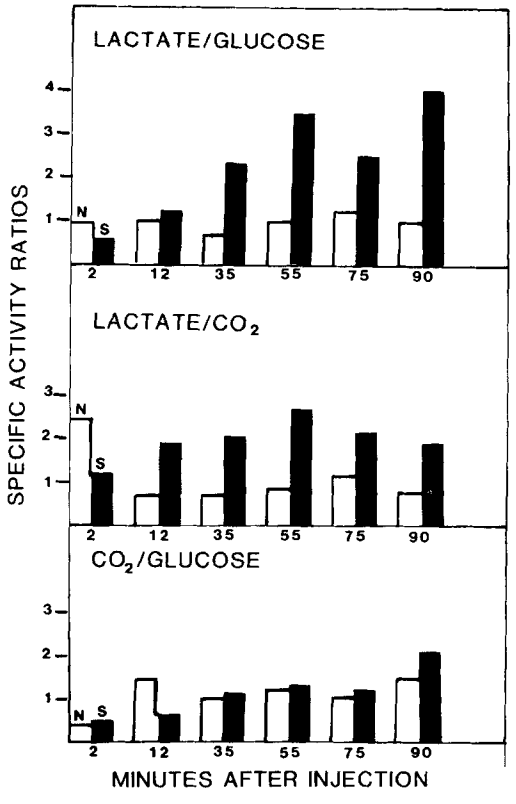

Fig. 2. Ratios of average specific activities of ^{14}C-lactate and $^{14}CO_2$ produced by brain to cerebral uptake of D-[3-^{14}C]-glucose at various time intervals after IV injection of D-[3-^{14}C]-glucose in control subjects (open bars) and chronic mental patients (solid bars). Values for ^{14}C-lactate/^{14}C-glucose, after 12 minutes, indicate production of much higher specific activity ^{14}C-lactate (product) from [3-^{14}C]-glucose (precursor) by mental patients' brains in vivo. With control subjects, ratios after early samples varied about theoretical value of 1.

arterial ^{14}C-lactate produced by peripheral metabolism of the D-[3-^{14}C]-glucose. If, for some reason, there were higher ^{14}C-lactate-specific activities in the arterial blood of the chronic mental patient, then, possibly, this lactate could be incorporated into the brain lactate pool; and, if arterial blood lactate-specific activities were falling more rapidly than those of the brain lactate pool, the ^{14}C-lactate added to the venous return blood by the brain would have higher specific activities than those of the arterial blood due to a "washout effect." We can discount this explanation readily by an examination of Figure 3 in which it is obvious that arterial lactate-specific activity values for mental patients were mostly *lower* than those of control subjects and that values *rose* with time after injection, thereby obviating the possibility of a "washout effect." A second explanation for the difference in brain-produced ^{14}C-lactate would be that there was a smaller pool of lactate in the schizophrenic brain which would result in higher specific-activity lactate being formed from the [3-^{14}C]-glucose. Again, this does not seem likely since, although a smaller pool of lactate could lead to higher specific activity entering the venous blood, it would necessarily mean also that there would be higher specific-activity pyruvate which would result in higher brain CO_2-specific activities than with normal subjects. That such was not the case was seen in previous reports [Sacks, 1965a, 1959] and in Figure 1, where brain CO_2-specific activities were seen to be mostly *lower* with mental patients. A third explanation would involve a small lactate compartment(s) in some specific region(s) of brain in which the decarboxylation of the endogenously formed [1-^{14}C]-lactate was partially inhibited. In this way, there could be a very rapid formation of high specific-activity lactate, shortly after injection, which would "leak" into the large pool of brain lactate and/or enter the brain venous blood. This could occur while the arterial lactate-specific activities were increasing slowly (Fig. 3) and thereby lead to brain-produced lactate-specific activities which were

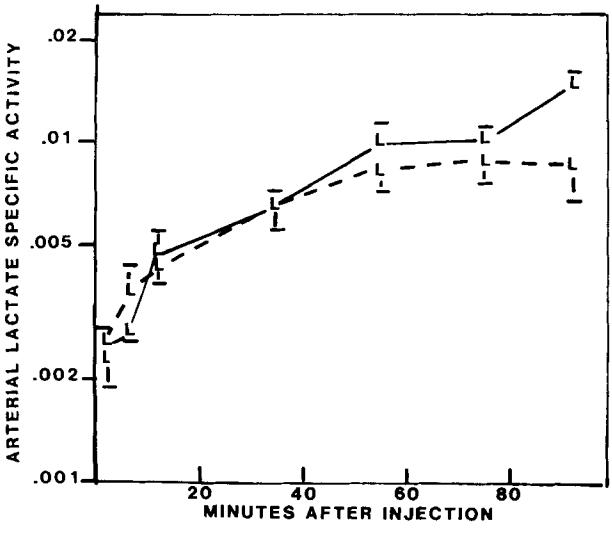

Fig. 3. Average specific-activity time curves for arterial whole blood ^{14}C-lactate produced peripherally following single IV injection of D-[3-^{14}C]-glucose in control subjects (solid lines) and chronic mental patients (dotted lines). Curves show similarity of values for two groups and indicate gradual increase in lactate-specific activities with time after injection.

greater than those of the arterial blood and larger than those of the ^{14}C-glucose taken up by the brain at that time. To date, this seems to be the most likely explanation for our data. Since V-A lactate differences (unlabeled) were very small, only a minute amount of high specific-activity lactate needed to be added to the venous blood to produce results such as those shown above. In a report which preceded most of our D-[3-^{14}C] glucose experiments [Sacks, 1961], we found average V-A differences of lactate were 0.47 mg % (0.052 mmole/liter) for mental patients and 0.55 mg % (0.061 mmole/liter) for control subjects. In this much smaller series, values were different; ie, for the 12 mental patients, the average V-A lactate difference was 0.144 mmole/liter; and, for the 12 control subjects, it was 0.084 mmole/liter. Although the average values were quite different, the great variability in results (ie, as seen above, there were even some A-V differences) made this difference statistically not significant. That higher lactate-specific activities were produced by mental patients' brains even with increased V-A lactate differences, emphasizes the significance of the difference between the two groups.

In order to estimate the effect of the peripheral formation of ^{14}C-lactate from the ^{14}C-glucose in our studies, we employed an experiment in which we administered DL-[2-^{14}C] lactate to a mental patient by constant infusion. Blood samples were drawn continuously. The resulting data (Fig. 4) demonstrate dramatically the constant uptake (A-V differences) of ^{14}C-lactate from arterial blood by brain and the consistent cerebral oxidation of the ^{14}C-lactate to $^{14}CO_2$ (V-A $^{14}CO_2$ differences). From them, we could estimate the average uptake of ^{14}C-lactate as 9% of the arterial values, so that it could be determined that cerebral uptake of the peripherally produced ^{14}C-lactate in our D-[3-^{14}C] glucose experiments could not have significantly affected the results seen above.

On finding this difference in the ^{14}C-lactate produced from [3-^{14}C] glucose by the brain of the mental patient, we reexamined the unpublished lactate data of two unusual studies with chronic psychiatric patients. One, S_{13}, had a brief convulsive seizure preceding the test period and the other, S_{14}, was considered as having early Parkinson's disease upon examination by a neurologist two weeks after the experiment (see Figures 4 and 5 of Sacks [1959]). Although in these experiments, the intravenously injected substrate was not D-[3-^{14}C] glucose (S_{13} was given [U-^{14}C] glucose and S_{14}, [1-^{14}C] glucose); the ^{14}C-lactate results were extraordinary and led us to speculate that these cases may represent more extreme examples of the difference in brain-produced ^{14}C-lactate than those of the 12 patients given [3-^{14}C]-glucose. Figure 5 shows specific-activity time curves for Experiment S_{13}, and Figure 6 summarizes the data of Experiment S_{14}. For comparison, we have included typical experiments using the same specifically labeled ^{14}C-glucose (Expts. S_4 and S_6). In both the S_{13} and S_{14} studies, the blood 'cold' lactate values and A-V differences were not unusual. From Figures 5 and 6, it is evident that the labeling of C_1 of lactate (curve L_1) of S_{13} and S_{14} was quite similar to values we usually found (Expts. S_4 and S_6).However, with C_2 and C_3 of lactate (curve $L_{2\&3}$), there was considerable ^{14}C activity in both arterial and venous blood samples. Theoretically, with [U-^{14}C] glucose as injected substrate, we would expect $C_2 + C_3$ to have twice the activity of C_1; and, with [1-^{14}C] glucose, we would expect all of the ^{14}C to be on C_3. That this labeling pattern did not usually occur, as evidenced in Experiments S_4 and S_6, indicates that in the human subject in vivo the peripheral metabolism of lactate does not follow the Embden-Meyerhof-Parnas (EMP) pathway only, but also involves considerable randomization due probably to recycling through the tricarboxylic acid cycle (TCA). It is of interest that in our unpublished experiments using the rat as an experimental animal, the labeling of the brain ^{14}C-lactate following injections of specifically labeled ^{14}C-glucose showed the theoretically expected patterns (ie, according to the EMP).

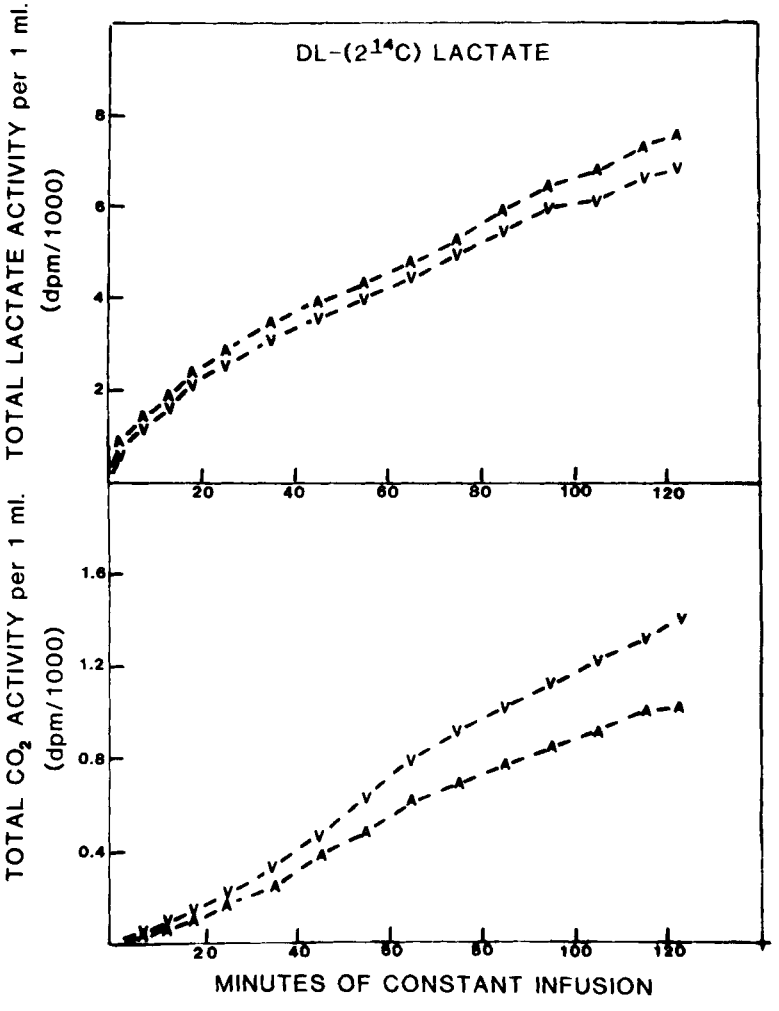

Fig. 4. Activity time curves for chronic mental patient given constant IV infusion of DL-[2-^{14}C] lactate. Arterio (A)-venous (V) blood samples were drawn continuously for five-minute intervals until 20 minutes after the start and at 10-minute intervals thereafter. Curves demonstrate constant uptake of ^{14}C-lactate by brain (ie, (A-V) ^{14}C-lactate differences) with continuous cerebral production of $^{14}CO_2$ [ie, (VA)] $^{14}CO_2$ differences).

Both experiments S_{13} and S_{14} were unusual in that initial arterial $^{14}CO_2$ values were very high and then fell rapidly before increasing again (Figs. 5, 6). Also, the three-minute blood sample in S_{14} had an unusually large (V-A) $^{14}CO_2$ difference, giving an extraordinarily high brain CO_2-speficic activity, and this was followed by four sets of blood samples which had (A-V) $^{14}CO_2$ *differences* indicating *no production of* $^{14}CO_2$ *by brain* during that time interval. In over 130 experiments using our arterio-venous technique with ^{14}C-glucose, this was the only time that we saw (A-V) $^{14}CO_2$ differences. In the S_{13} experiment, the three-minute sample had the expected (V-A) $^{14}CO_2$ difference, but this was followed by decreas-

ing differences, so that brain CO_2-specific activities fell rapidly until the 30-minute sample. The resulting brain CO_2-specific activity curve I was unlike any which we have seen for a [U-^{14}C] glucose experiment. If we consider experiments S_{13} and S_{14} as extreme cases of the difference described above, we can offer a rationale for these extraordinary results. If the decarboxylation of lactate in the small pool(s) were more inhibited and more widespread than in the 12 mental patients in our [3-^{14}C] glucose study, the initial specific activities could be much higher; and, therefore, the ^{14}C-lactate entering the venous blood could conceivably raise blood activities sufficiently to account for the unusually high arterial ^{14}C-lactate and $^{14}CO_2$. Assuming the lactate-labeling pattern of the human brain to be similar to that of the rat in that it follows the EMP pathway, this highly labeled lactate would be labeled on $C_2 + C_3$ in the S_{13} experiment and on C_3 in the S_{14} study. Although our method did not separate C_2 from C_3, from Figures 5 and 6, we can see that there were very high ^{14}C activities on these two carbon atoms in both experiments. Based upon our studies using specifically labeled ^{14}C-lactate as injected substrates [Sacks, 1965b], the very high arterial lactate-specific activity values found in S_{13} and S_{14} could readily result in the very high initial arterial $^{14}CO_2$-specific activities in these experiments. In addition, it is more likely that the arterial ^{14}C-lactate values were even higher initially than those seen in our earliest (20 minute) sampling due to the uptake by the brain of extremely high specific-activity ^{14}C-glucose immediately after the pulse injection of ^{14}C-glucose. Thus, the specific activity of the brain lactate would be very highly labeled in the early moments of the experiment and would then fall rapidly due to the exponential decline of the precursor (^{14}C-glucose). At the same time, the arterial blood lactate-specific activity might be expected to be very high initially, fall rapidly, and then increase slowly and perhaps, near the end of the 90-minute study, might even decline somewhat. In our experiments using a single injection of DL-[1-^{14}C] lactate [Sacks, 1961, 1965b], we saw that arterial $^{14}CO_2$-specific activities rose very rapidly and exceeded those of brain CO_2. Thus, we know that lactate injected into the blood stream can be decarboxylated peripherally quite rapidly. Since in S_{13} and S_{14} arterial lactate was labeled on C_2 and/or C_3, the very highly labeled ^{14}C-lactate "leaking" into the venous blood in the early moments of the study would be rapidly decarboxylated, yielding acetyl coenzyme A labeled on C_1 and/or C_2 of the acetyl moiety. This could then enter the brain and be metabolized by way of the TCA, bypassing the hypothetical partial metabolic block at the lactate-pyruvate step. Then, as the arterial ^{14}C-lactate fell rapidly early in the study, the contribution of the arterial ^{14}C-acetyl coenzyme A to brain $^{14}CO_2$ would decrease rapidly to levels which would affect brain $^{14}CO_2$ only slightly. At the same time, that brain ^{14}C-lactate (labeled on C_2 and/or C_3) which managed to get through the partial block and enter the TCA would gradually contribute to brain $^{14}CO_2$ in the usual manner (see Figure 5 of Sacks [1965b]), so that after about 30 minutes the brain CO_2-specific-activity curve I would start to rise. With mental patient S_{14}, we would assume a more extensive and more widespread inhibition of the conversion of lactate to pyruvate.

Both of these mental patients were reexamined using conditions identical to those of the first experiments. The repeat studies yielded data which followed the pattern of experiments with other mental patients and did not resemble the aberrant results of the original studies. Further, patient S_{14} who was thought to have early Parkinson's disease, never did develop that illness. Since S_{13} did not experience another seizure in the repeat study, we are inclined to believe the unusual results were due to that event; however, the reason for the difference between the first and second experiments with patient S_{14} remains unknown. Possibly, he was tested originally during a period of extreme mental disturbance.

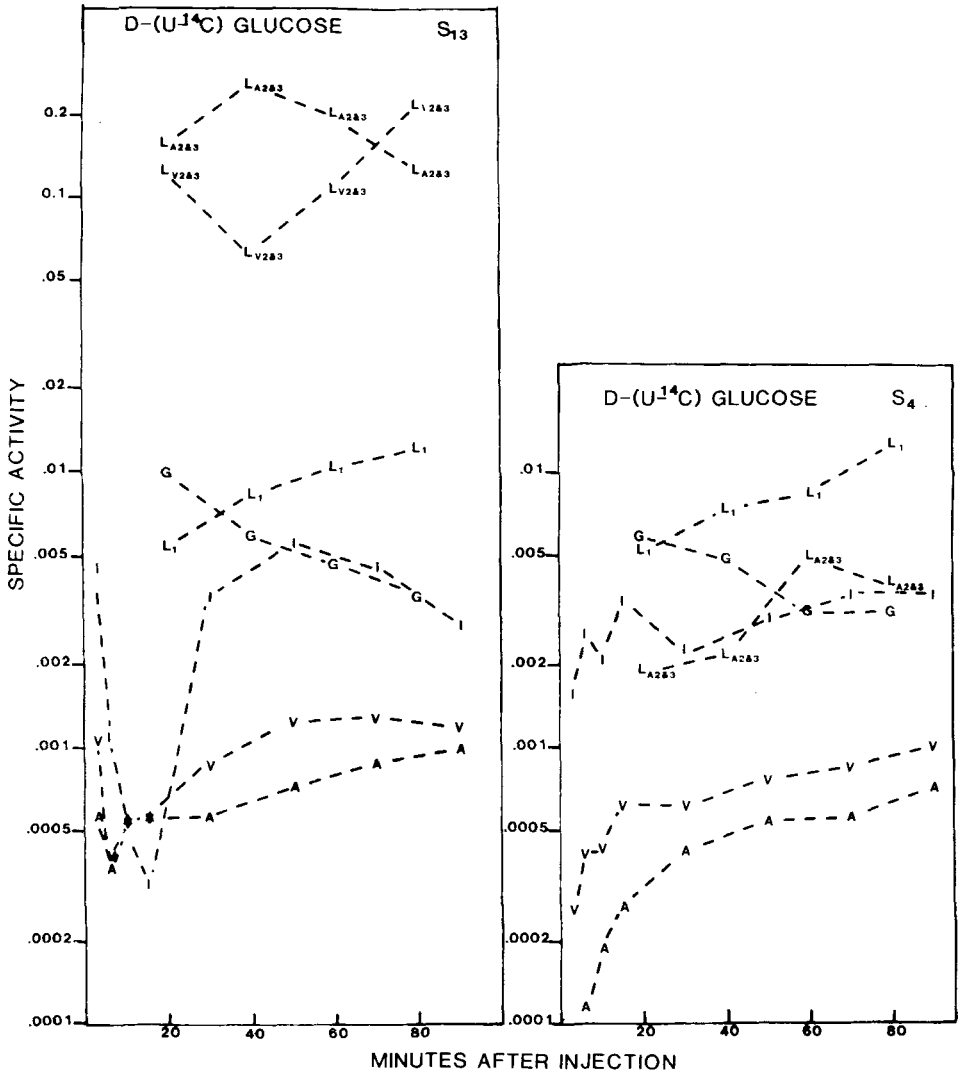

Fig. 5. Specific-activity time curves (plotted semilogarithmically) for patient S_{13} given D-[U-^{14}C] glucose by single IV injection. Patient experienced a brief, convulsive seizure preceding the test [Sacks, 1959]. Curves A and V represent arterial (femoral) and venous (superior bulb of internal jugular) CO_2-specific activities, respectively. Curve I gives specific activity of CO_2 produced by brain [Sacks, 1957]. Curve G shows specific activity of glucose taken up by brain (see text). Curve L_1 gives specific activity of C_1 of lactate in arterial whole blood. Curves $L_{A2\&3}$ and $L_{V2\&3}$ represent specific activity of $C_2 + C_3$ of lactate in arterial and venous whole blood, respectively. Specific-activity time curves (right) for chronic mental patient S_4 are representative of data usually found with D-[U-^{14}C] glucose as injected substrate.

Theoretically, the decarboxylation of lactate occurs after it is reconverted to pyruvate, which is then decarboxylated through the action of the pyruvate dehydrogenase complex with thiamine pyrophosphate as a coenzyme. Unfortunately, in this series of experiments with [3-^{14}C] glucose, insufficient (A-V) ^{14}C-pyruvate determinations were per-

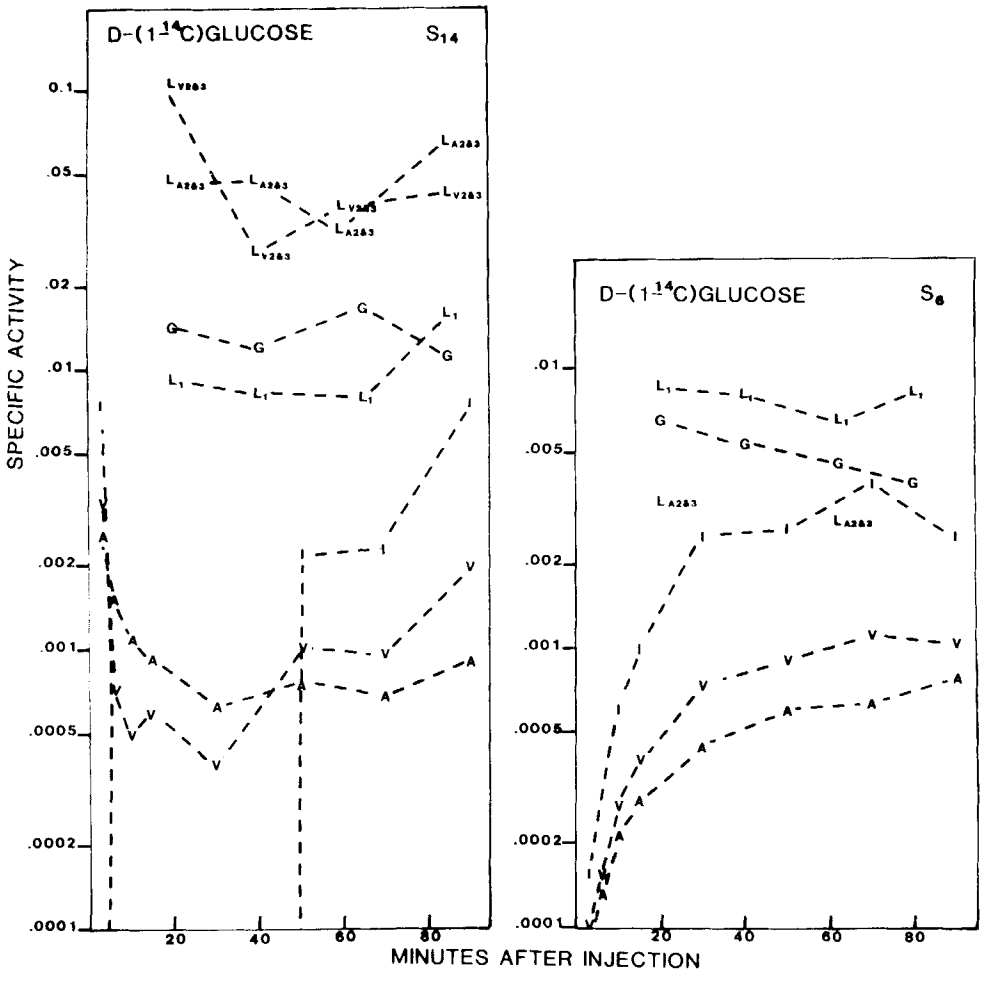

Fig. 6. Specific-activity time curves for psychiatric patient S_{14} given a single IV injection of D-[1-^{14}C] glucose. S_{14} was considered as having early Parkinson's disease upon examination by a neurologist two weeks after experiment [Sacks, 1959], but never did develop that illness. Curves are represented as in Figure 6. Specific-activity time curves (right) for chronic mental patient S_6 are typical of those resulting after injection of D-[1-^{14}C] glucose.

formed to evaluate cerebral pyruvate decarboxylation. However, in an earlier report from this laboratory [Sacks, 1961], experiments with three chronic mental patients and three control subjects given [1-^{14}C] pyruvate were described. In that study, it was evident that brain CO_2-specific activity values were higher at three and six minutes with normal subjects, suggesting that [1-^{14}C] pyruvate decarboxylation was somewhat inhibited in mental patients.

The relationship of lactate and pyruvate, both of which are added to blood as it flows through the brain [Sacks, 1961, 1965b; Kneinerman et al, 1958; Rowe et al, 1965; Gottstein et al, 1963; Otani, 1963; Sato et al, 1963], to mental disturbances is well known. A de-

ficiency of thiamine, the precursor for the coenzyme thiamine pyrophosphate, leads to disturbances of carbohydrate metabolism, especially in the brain. Ultimately, such deficiency results in diseases known as beri-beri and Wernicke's encephalopathy which are characterized as defects of the central nervous ysstem. In patients having chronic familial illness known as anxiety neurosis, infusions of sodium lactate reportedly induce anxiety symptoms and attacks [Pitts and McClure, 1967; Pitts, 1969].

Earlier investigations by our laboratory have indicated that less of the brain CO_2 was derived from glucose in psychotic subjects, and it was thought this was due either to a decreased oxidation of carbohydrate by brain or to a dilution of one or more carbohydrate intermediates by some protein and/or lipid intermediate occurring at some stage(s) above the TCA [Sacks, 1959; 1961]. Now, we would believe less $^{14}CO_2$ was produced from ^{14}C-glucose by the brain of the chronic mental patient as a result of the partial inhibition of the decarboxylation of the endogenously formed ^{14}C-lactate and the subsequent "leaking" of part of it into the brain's venous blood.

It is logical to assume that our data could have been influenced by differences in institutionalization and in diet in the two groups. However, since the arterial curves, which are indicative of overall body metabolism, showed no real variations between the two groups, these factors were probably of little significance.

The importance of the difference in the chronic mental patients' in vivo cerebral production of [1-^{14}C] lactate from D-[3-^{14}C] glucose in the etiology of schizophrenia remains to be seen. Perhaps with more modern techniques such as the use of Positron Emission Transverse Tomography with specifically labeled ^{11}C-glucose we may be able to elaborate further on this matter.

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