posed not to continuous light but to a photoperiod that will ensure synchrony in locomotion and pheromone release with native weevils. Also, trap formulations of grandlure must have release rates equivalent to or greater than the peak release of pheromone by native males.

The role of light in pheromone release is consistent with field observations of boll weevil behavior. Artificial light could possibly be introduced into a field at night, as in an orchard, to alter rhythms of pheromone release and so to interfere with mating behavior of pest insects. The use of proper LD cycles in the insectary might also enhance the field performance of sexually sterile insects in the "sterile-male" approach to insect control.

We believe that chemical cues that play a part in insect attractants as related to sexual responses and host-parasite-predator behavior may, in general, be mediated by rhythms such as those observed in the specific case of the male boll weevil pheromone.

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11. A stainless steel column (76 m by 0.76 mm inner diameter) coated with OV-17 was used at 160°C isothermally. The nitrogen flow was 8 ml/min.
12. The survival rate of male weevils rendered sexually sterile by irradiation is about 50 percent in 10 days. The survival rate in our study of the four replicates under the LD cycle was 84.4 percent in 20 days; under DD, survival for 20 days was 64.8 percent; under LL, survival for 20 days was 72 percent.
13. Over the 20-day test period, weevils held under the DD cycle produced 3.8 μg of pheromone per weevil, while those under the 16 : 8 light regimen produced 50.5 μg of pheromone per weevil.
14. Data of G. McKibben indicate a slow loss of pheromone from feces collected ½ hour after being excreted.
15. We thank B. Boyd for assistance in analyzing the samples and calculating the data.

28 March 1977; revised 22 August 1977

Measurement of Regional Substrate Utilization Rates by Emission Tomography

Abstract. *Emission tomography can be used to monitor, in vivo and regionally, the utilization of metabolic substrates labeled with positron-emitting radioisotopes produced by a cyclotron. The concept was validated by measuring brain glucose utilization with carbon-11-labeled glucose in rhesus monkeys.*

Present methods of studying organ metabolism in vivo have serious shortcomings. The appearance of linear accelerators and cyclotrons in the medical environment and the parallel development of rapid chemical techniques for incorporating their products into compounds have resulted in the availability of a large number of radioactively labeled substrates (*1*). When these labeled substrates are used with recently developed imaging systems employing the concept of positron emission tomography (*2*), the resulting data make it possible to calculate values for several parameters of physiological significance, using a mathematical model developed by Raichle *et al.* (*3*). This approach is analogous to quantitative autoradiography, but has the added advantage of allowing studies in vivo.

In this report we describe the basis for a low-risk, quantitative method of measuring glucose utilization regionally in vivo in the human brain. The method employs emission tomography to externally monitor the spatial distribution in brain of ^{11}C-labeled glucose, but is sufficiently general to be used with radioglucose or other radiolabeled pharmaceuticals in other organs. The data for our report were obtained on seven adult rhesus monkeys.

The monkeys were anesthetized with phencyclidine, paralyzed with gallamine, and passively ventilated with 100 percent oxygen. A peripheral artery was catheterized for measuring the specific activity of [^{11}C]glucose in blood. The monkeys were placed in an emission tomograph (*2*) and images of single transverse sections of brain tissue about 1.5 cm thick were obtained (Fig. 1). Because of the small size of the monkey brain relative to a resolution element of the imaging system (1.5 cm^3), data from several resolu-

Table 1. Measurements of the cerebral metabolic rate for glucose (Φ) and the cerebral blood volume (V_b) in seven adult rhesus monkeys by using quantitative emission tomography, [^{11}C]glucose, and [^{11}C]carboxyhemoglobin. Plasma glucose concentrations (C_b) were measured by standard enzymatic methods. Values in the last row are means ± standard deviations.

Φ (mg per 100 g min^{-1})	V_b (ml per 100 g)	C_b (mg per 100 ml)
4.51	4.5	65
4.59	4.1	78
4.90	3.9	83
4.93	4.0	86
6.80	4.4	132
5.08	4.2	80
5.67	4.2	115
5.21 ± 0.80	4.1 ± 0.2	96 ± 22

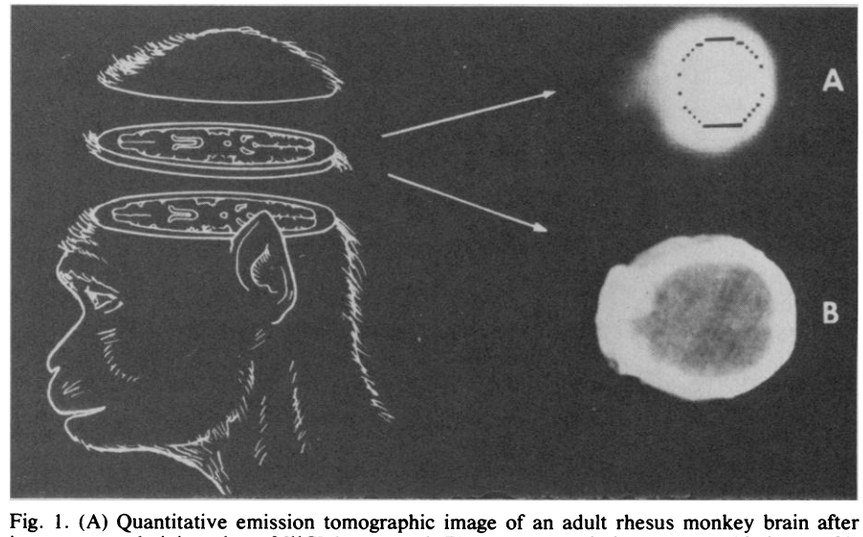

Fig. 1. (A) Quantitative emission tomographic image of an adult rhesus monkey brain after intravenous administration of [^{11}C]glucose and (B) x-ray transmission tomographic image (80-second scan with an 8-mm collimator on an EMI CT 5000 prototype body scanner) at the same level for comparison. The accompanying drawing shows the approximate anatomical orientation of the images.

0036-8075/78/0303-0986$00.50/0

tion elements were summed to give an average value for the brain slice. The radioglucose, which was injected intravenously, was prepared for this study by a modification of the technique described in (*4*). The specific activity of glucose in arterial blood was monitored every 15 seconds for the first minute after injection and every half-minute thereafter. Collection of data for an image was begun 4 minutes after injection of the radioglucose and continued for 2 minutes. The arterial blood samples were counted in a well counter. Detection efficiencies were measured by using appropriately designed and calibrated phantoms (*5*). The data were analyzed by using a mathematical model that has been applied successfully in studies of brain glucose metabolism and transport (*3*). The model was modified for the present emission tomography studies (*6, 7*).

Cerebral blood volume was measured in each monkey by causing it to inhale the gas ^{11}CO, thereby forming in vivo the vascular tracer [^{11}C]carboxyhemoglobin (*8*). This measurement was used to correct the scan data for the [^{11}C]glucose present in the brain vascular compartment during the scan.

A typical emission tomographic image of a monkey brain is shown in Fig. 1. Quantitative data are shown in Table 1. The glucose utilization rates compare favorably with values obtained by others in monkeys and humans (*9*). Furthermore, they demonstrate that our model (*6*), previously validated for use with a conventional detection system (*3*), can now be employed with emission tomography in a safe, quantitative manner for the measurement in vivo of truly regional organ metabolism in monkeys and in humans.

We wish to emphasize several important features of our approach. First, we employ a tracer that is biochemically identical to the compound being traced. This is not the case with other tracers that have been proposed (*10*), which are analogs of the parent compounds (for instance, 2-deoxy-D-glucose). With the analogs corrections must be made in the tracer model for differences in transport properties and enzyme affinities, which vary among species (*10*). Such corrections may present an added difficulty when the organ of interest is diseased. Second, the measurement we propose requires a relatively short time, so that repeated measurements can be made during the course of one experiment should they be required for the evaluation of transient phenomena. Third, our method is not restricted to [^{11}C]glucose or to the brain. The approach is sufficiently general to be employed with a variety of available radiopharmaceuticals utilized by brain, heart, or other organs. Finally, where only a relative mapping of regional utilization rate is sought within an organ of interest, sampling of peripheral arterial blood is not necessary.

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2. Emission tomography is a visualization technique in nuclear medicine that yields an image of the distribution of a previously administered radionuclide in any desired transverse section of the body. Positron emission tomography utilizes the unique properties of the annihilation radiation generated when positrons are absorbed in matter. It is characterized by the fact that an image reconstructed from the radioactive counting data is a highly faithful representation of the spatial distribution of a radionuclide in the chosen section [E. J. Hoffman, M. E. Phelps, N. A. Mullani, C. S. Higgins, M. M. Ter-Pogossian, *J. Nucl. Med.* **17**, 493 (1976)].
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6. In our model (*3*) it is assumed that over the duration of the experiment no ^{11}C-labeled metabolites of radioglucose leave the field of view of the external radiation detector (*7*). At any particular instant, therefore, the response of the detector is assumed to be due to ^{11}C distributed between unmetabolized radioglucose in blood, in brain interstitial fluid, and in all the labeled metabolites formed in the brain from the beginning of the experiment. We have shown (*3*) that in the systemic steady state these assumptions lead to the global tracer conservation equations

$$q(t) = q_b(t) + q_i(t) + q_m(t) \quad (1)$$

$$\dot{q}_m(t) = \Phi a_i(t) \quad (2)$$

and

$$\dot{a}_i(t) + \kappa a_i(t) = \kappa a_b(t) \quad (3)$$

For the present study we assumed further that these relations remain valid for regional measurements. Thus, in Eqs. 1 to 3 the q's represent local molar masses of radioglucose or radiocarbon within a spatial resolution element of the detector; the a's represent radioglucose specific activities; and the subscripts b and i denote the blood and interstitial fluid compartments, respectively. Because we assume blood and interstitial fluid to be glucose compartments, radioglucose specific activities are taken as spatially uniform within a compartment throughout the entire detector field of view. The subscript m refers to ^{11}C on radioglucose metabolites. The symbol Φ represents the regional net transport rate of systemic glucose from blood to brain tissue, or equivalently, the glucose utilization rate within a detector resolution element of the emission tomograph. The rate constant κ is the sum of the two compartmental rate constants for egress of glucose from interstitial fluid to blood and to the metabolic pathways. The variable t signifies time elapsed from the beginning of radioglucose injection, and also serves to identify time-dependent tracer quantities. The overdots denote time derivatives.

With the initial condition of no tracer anywhere within the detector field, the solutions of Eqs. 2 and 3, together with Eq. 1, lead to the following expression for the glucose utilization rate

$$\Phi = \frac{q(t) - C_b V_b a_b(t)}{\int_0^t a_b(u)du + \frac{1}{\kappa(\alpha - 1)} a_i(t)} \quad (4)$$

In Eq. 4, the interstitial-fluid specific activity is obtained in terms of blood specific activity as the solution of Eq. 3 in the form

$$a_i(t) = \kappa e^{-\kappa t} \int_0^t e^{\kappa u} a_b(u)du$$

The additional parameter α denotes the ratio of forward to reverse unidirectional systemic glucose fluxes across the blood-brain barrier (*3*); C_b is the glucose concentration in plasma; and V_b denotes the local volume of blood in a detector resolution element of the emission tomograph [milliliters per 100 g; see (*8*)]. All quantities in Eq. 4 can be measured experimentally or inferred from the data by using statistical parameter-estimation techniques. However, for the present study we selected as values for α and κ the means of previously measured values [1.37 and 0.034^{-1}, respectively; (*3*)] because Φ (Eq. 4) is relatively insensitive to variation in α and κ. The regional ^{11}C molar mass $q(t)$ in Eq. 4 is the instantaneous value; in practice, however, decay counts are summed over a finite period, usually 2 to 4 minutes. To reflect this and to make use of all data collected in the image, we integrated Eq. 4 over the time of the scan. In place of the instantaneous count rate, proportional to $q(t)$, the result involves the total number of radioactive decay events observed during the scan period. To use the new relation, we applied appropriate instrumental calibration factors (*5*) and corrected the counting data for radioactive decay of ^{11}C.
7. Estimates of the loss of radiolabeled CO_2 from the brain following the administration of radiolabeled glucose that are based on the work of others [R. A. Hawkins, A. L. Miller, J. E. Cremer, R. L. Veich, *Neurochemistry* **23**, 917 (1974); R. Balazs, in *Handbook of Neurochemistry*, A Lajtha, Ed. (Plenum, New York, 1970), vol. 3, pp. 1–34] as well as on our own results (unpublished) suggest that no more than 5 to 6 percent of our tracer is lost by this route during the 6 minutes required to make our measurement.
8. The tissue blood volume (V_b) was determined from data obtained from the equilibrium tomographic image of [^{11}C]carboxyhemoglobin in brain (counts per second per milliliter of tissue) and venous blood samples (counts per second per gram of blood) obtained during the time of the emission scan. The quantity V_b (milliliters per 100 g) was calculated from

$$V_b = \frac{[\text{count sec}^{-1}\ (\text{ml tissue})^{-1}] \times 100}{[\text{count sec}^{-1}\ (\text{g blood})^{-1}] \times \rho \times \delta \times f}$$

where ρ is the density of blood (~1.05 g/ml), δ is the tissue density (~1.05 g/ml), and f is the ratio of the mean tissue hematocrit to the large vessel hematocrit [~0.85; J. O. Eichling, M. E. Raichle, R. L. Grubb, Jr., K. B. Larson, M. M. Ter-Pogossian, *Circ. Res.* **37**, 707 (1975)].
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11. This work was supported by NIH grants HL 13851, NSO 6833, and RR 00396 and Teacher-Investigator Award NS 11059 (M.E.R.). We thank R. Feldhaus, C. Cooper, J. Mazanec, and the staff of the Washington University Medical School Cyclotron.

9 August 1977; revised 25 October 1977