(Table 1). These changes accompanied the increased de novo formation of the protein and lipid components of the microsomal membrane.

It is well known that the apparent microviscosity of the lipid bilayer of model and biological membranes diminishes by increasing the phospholipid to cholesterol molar ratio (*10*). Increases in the degree of unsaturation of the phospholipid acyl chains, or in the molar ratio of phosphatidylcholine to sphingomyelin, may also decrease the membrane apparent microviscosity (*10*). In this respect Feuer (*11*) recently reported a significant perinatal increase in the production of liver microsomal phosphatidylcholine with an increasingly higher proportion of unsaturated fatty acids. The changes observed at birth in the apparent microviscosity of the microsomal membrane may be important in the perinatal regulation of biological activities that are associated with this membrane. The activity ratio of "native" (nonactivated) to detergent-activated UDPGT in fetal liver is higher than in adult liver (*12*). This could possibly be explained by an increased exposure of the enzyme in the more rigid fetal membrane (*13*). Results from our laboratory indicate that fluidization of fetal rat liver microsomal membranes by phosphatidylcholine enrichment reduces the activity of "native" UDPGT.

The present findings may also be relevant to other membrane-bound enzyme systems and membrane proteins, in liver microsomes or in other hepatic or extrahepatic organelles, the action of which is affected by the membrane fluidity. Recently, a significant increase in membrane fluidity similar to that observed in the present study was also reported for the plasma membrane of chick heart between the last day of embryonic life and adulthood (*14*). It was suggested (*14*) that the changes in membrane fluidity may contribute to developmental changes in the uptake of sugars, amino acids, and urea by the heart cells.

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References and Notes

1. A. H. Neims, M. Warner, P. M. Loughnan, J. V. Aranda, *Annu. Rev. Pharmacol. Toxicol.* **16**, 427 (1976); O. Greengard, *Pediat. Res.* **11**, 669 (1977); G. J. Dutton, *Annu. Rev. Pharmacol. Toxicol.* **18**, 17 (1978).
2. S. Eletr, D. Zakim, D. A. Vessey, *J. Mol. Biol.* **78**, 351 (1973).
3. A. Y. H. Lu and W. Levin, *Biochem. Biophys. Res. Commun.* **46**, 1334 (1972).
4. O. H. Lowry, N. J. Rosebrough, A. L. Farr, R. J. Randall, *J. Biol. Chem.* **193**, 265 (1951).
5. M. Shinitzky and Y. Barenholz, *ibid.* **249**, 2652 (1974).
6. V. I. Teichberg and M. Shinitzky, *J. Mol. Biol.* **74**, 519 (1973).
7. H. Folch, M. Lees, G. H. Sloane-Stanley, *J. Biol. Chem.* **226**, 497 (1957).
8. G. R. Bartlett, *ibid.* **234**, 466 (1959).
9. Y. Barenholz, E. J. Patzer, N. F. Moore, R. R. Wagner, in *Enzymes of Lipid Metabolism*, S. Gatt, L. Freysz, P. Mandel, Eds. (Plenum, New York, 1978), p. 45.
10. M. Shinitzky and Y. Barenholz, *Biochim. Biophys. Acta* **515**, 367 (1978).
11. G. Feuer, *Res. Commun. Chem. Pathol. Pharmacol.* **22**, 549 (1978).
12. J. Kapitulnik, M. Tshershedsky, Y. Barenholz, in preparation.
13. M. Shinitzky and B. Rivnay, *Biochemistry* **16**, 982 (1977).
14. H. Kutchai, Y. Barenholz, T. F. Ross, D. E. Wermer, *Biochim. Biophys. Acta* **436**, 101 (1976).
15. This work was supported in part by a grant from the Joint Research Fund of the Hebrew University and Hadassah and by grant HL-17576 from the Public Health Service. We thank Drs. Dov Lichtenberg and Marta Weinstock for helpful discussions and Dr. M. Shinitzky for use of the instrument for measurement of fluorescence polarization.

10 April 1979; revised 2 July 1979

Tumor Location Detected with Radioactively Labeled Monoclonal Antibody and External Scintigraphy

Abstract. *Murine teratocarcinomas were located in mice by external gamma-ray scintigraphy with an iodine-125-labeled monoclonal antibody specific to the tumors. The specificity of the method was increased by subtracting the radiation produced by an iodine-125-labeled indifferent monoclonal antibody of the same immunoglobulin class as the tumor-specific antibody.*

The use of specific antibodies for tumor localization and treatment has been suggested and attempted for some time (*1*, *2*), with little success until recently. The main difficulties have been in the preparation and purification of specific antibodies to tumors and the suppression of background caused by unbound antibody or circulating antibody-antigen complexes.

Belitsky *et al.* (*3*) have successfully imaged both primary tumors and metastases in man by using ^{131}I-labeled immunoglobulin G (IgG) from absorbed goat antiserums to human renal carcinomas; these authors noted problems caused by the presence of a radioactive background due to a large excess of radioactively labeled nonspecific antibody. Goldenberg *et al.* (*2*) minimized some of these problems by combining ^{131}I-labeled affinity-purified goat antiserum to carcinoembryonic antigen (CEA) with a second radiolabel that remained in the general circulation (metastable technitium system: $^{99m}TcO_4$ and ^{99m}Tc-labeled serum albumin). The second radiolabel was distinguishable from the first by two-channel γ-ray scintigraphy; its image could therefore be subtracted from that of the radiolabeled tumor-specific antibody to provide a correction for unbound or metabolized antibody. Images of several human tumor types were obtained. Their results strongly support the possibility of using radiolabeled antibody for the detection of tumors and metastases, even those located deep within the body.

A more incisive approach is made possible by the recent development of monoclonal tumor-specific antibodies (*4*–*7*). Such antibodies, derived from lymphocyte hybridomas (*8*), are homogenous, require little labor for purification, and can be reproducibly prepared

Table 1. Accumulation of tumor antibodies in teratocarcinoma and selected organs. Five BALB/c mice, previously innoculated with MH-15 teratocarcinomas, were injected with ^{131}I-labeled tumor-specific antibody as described in the legend to Fig. 1. Lugol's solution (Lyne; two drops per 100 ml in drinking water) was administered to prevent accumulation of free iodine. After 48 hours the mice were killed and examined. Inspection revealed no metastases. Listed tissues were removed, weighed, and their radioactivity was determined. Specific activities represent means (± S.E.) of organs from separate mice; tumor to tissue ratios (means ± S.E.) were determined for each mouse, then averaged.

Tissue	Specific activity (cpm/mg)	Tumor to tissue ratio [(cpm/mg in tumor)/(cpm/mg in tissue)]*
MH-15 teratocarcinoma	41.7 ± 5.6	1.0
Thymus	8.1 ± 0.98	5.8 ± 1.6
Spleen	5.9 ± 1.2	5.1 ± 0.85
Liver	16.1 ± 1.7	2.55 ± 0.16
Heart	6.0 ± 0.76	7.2 ± 0.96
Lung	11.0 ± 1.6	3.8 ± 0.55
Forelimb muscle	3.3 ± 1.5	24. ± 9.4
Blood	31.7 ± 3.0	1.3 ± 0.21
Brain	1.16 ± 0.15	39.8 ± 9.3
Kidney	9.6 ± 1.5	4.7 ± 0.88

*In a separate experiment, two mice bearing P3-X63-Ag8 myelomas and MH-15 teratocarcinomas of equal size were similarly injected and killed. The tumor to tissue ratios of special interest were, respectively, MH-15/P3 = 1.92, 4.43; MH-15/liver = 1.00, 0.81; MH-15/spleen = 1.48, 1.41; and MH-15/muscle = 14, 21. That is, P3 myeloma tissue accumulates about as much antibody as other highly vascularized tissues.

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in large quantities. It should then be possible to use a monoclonal, nonselected antibody of the same class as the tumor-specific antibody for background subtraction. If both antibodies were labeled in similar fashion with different radioisotopes of the same element, metabolism of the two should be similar, except for binding to tumors. We here report results that indicate that tumor imaging by radiolabeled monoclonal antibody is feasible, with and without such background subtraction.

Tumors were induced in mice by subcutaneous injection of 10^6 teratocarcinoma cells in one thigh and 2×10^6 myeloma cells in the other in the same animal (Fig. 1a). Tumor-bearing animals were subsequently injected with ^{131}I-labeled teratocarcinoma-specific antibody, with ^{123}I-labeled indifferent antibody, or with a mixture of both as identified in Fig. 1a. Scintigraphic results indicated that much of the ^{131}I (teratocarcinoma-specific antibody, Fig. 1b) and the ^{123}I (indifferent antibody, Fig. 1c) was in the general circulation, thyroid, and liver. We believe this was due to persistence of unbound antibody in circulation and to normal metabolism of both antibodies. This whole-body radioactive background could be considerably reduced by subtracting the radioactivity caused by the indifferent antibody from that of the tumor-specific antibody (Fig. 1d); after subtraction, it was clear that tumor-specific antibody was preferentially localized within the teratocarcinoma. No significant binding of either antibody to the control myeloma was detectable. The preferential concentration of tumor-specific antibody within the teratocarcinoma was confirmed by determining the relative amount of ^{131}I in tumors and other organs of animals that were injected with ^{131}I tumor-specific antibody, killed at 48 hours, and autopsied (Table 1).

In our system, with the use of background subtraction, adequate localization occurs between 24 and 48 hours after injection of labeled antibodies. During this time, much of the radiolabel in both tumor-specific and indifferent antibodies is excreted, presumably in part through metabolic breakdown. This clearance of unbound antibody makes it possible to locate tumors without background subtraction at 4 to 5 days after injection (Fig. 2).

The myeloma was chosen as a control for nonspecific antibody binding because it does not bind teratocarcinoma-specific antibody and because its overall growth characteristics resemble those of the teratocarcinoma. Both tumors are composed of tightly packed, small cells; in this one case, at least, changes in microvascularity or other nonspecific processes do not appear responsible for the concentration of specific antibody in teratocarcinomas. Moreover, the teratocarcinomas do not concentrate indifferent IgM. These two data indicate that we are indeed dealing with a specific interaction of tumor and antibody to tumor.

We believe that our results demonstrate the practicality of using monoclonal antibodies to locate tumors. The use of hybridoma-derived antibodies avoids the necessity of performing tedious absorptions against normal tissues to eliminate spurious binding, and the need to perform affinity chromatography against specific tumor antigens (which are usually lacking) to produce purified antibody. Once prepared, hybridomas potentially offer a reproducible, large-scale source of uniform monospecific antibody, free of the variability usually found in repeated animal immunizations. Moreover, the use of an indifferent monoclonal antibody of the same class as the specific antibody in question, labeled in chemically identical but isotopically distinct fashion, permits a logical approach to the subtraction of background radioactivity caused by circulation and metabolism of excess tumor-specific antibody. Finally, the purity of monoclonal antibodies permits the use of a minimum amount of radiolabel for tumor detection, since potentially all of the antibody is tumor-directed (except for some inactivation that occurs during labeling).

This approach, however, necessitates the preparation of antitumor hybridomas and extensive screening of their antibody products against normal tissues. Whether antitumor hybridomas can be prepared against most tumors remains to be

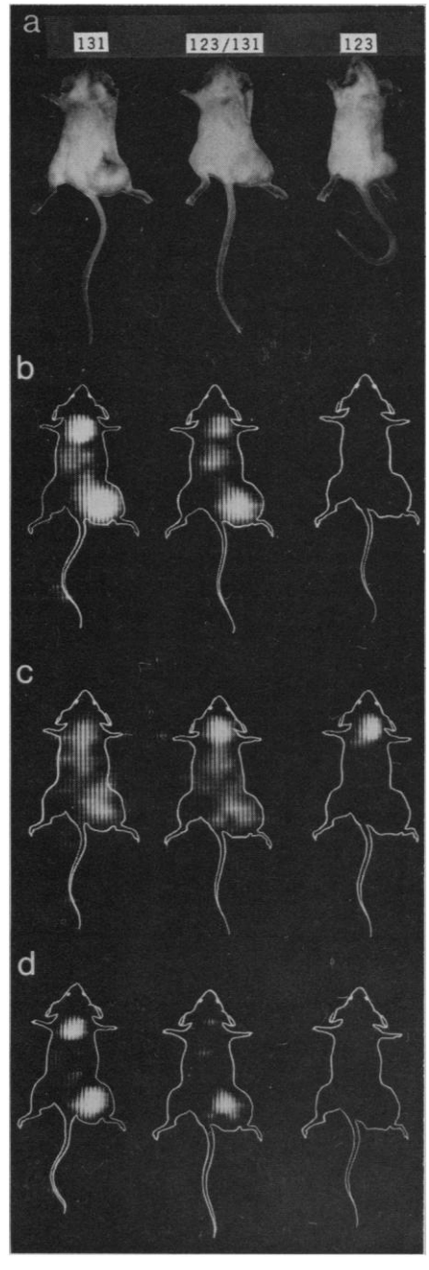

Fig. 1. (a) Mice arranged for gamma-ray scintigraphy 50 hours after injection. Each mouse has a teratocarcinoma in the right thigh and a myeloma in the left thigh. Mice were injected with ^{131}I-labeled specific antibody, or ^{123}I-labeled indifferent antibody, or a mixture of both. (b) "Raw" ^{131}I image. (c) "Raw" ^{123}I image (indifferent antibody and spillover from tumor-specific antibody). (d) Iodine-131 image from which "true" ^{123}I image has been subtracted. Tumors were induced and radiolabeled antibodies were prepared as described in the text. Typical specific activities were 10 to 30 μCi of ^{131}I per microgram of tumor-specific antibody and 100 to 500 μCi of ^{123}I per microgram of indifferent antibody. Ten micrograms of each antibody in 100 μl of phosphate-buffered saline was injected into the tail veins (100 to 300 μCi of ^{131}I-labeled antibody to SSEA-1 or 2 to 3 mCi of ^{123}I-labeled ABPC-22). The larger amount of radioactivity in ^{123}I-labeled antibody was chosen to compensate for the shorter half-life of this isotope ($t_{1/2}$ = 13.2 hours). Mice were anesthetized for imaging by intraperitoneal injection of Nembutal (Abbott). Scintigraphy was done by means of a Picker Dyna Camera model 415 LFOV with a medium-energy parallel-hole collimator. Scintigraphic data were recorded and analyzed on a Medical Data Systems computer and displayed as a linear color-scaled television image (converted to a less informative gray-scale image for this figure). This system can show the image produced by ^{131}I alone, ^{123}I alone, or a composite image from any multiple of the two. Images were recorded in both ^{131}I (364 keV) and ^{123}I (159 keV) peaks at the time of injection and at 4 to 5 hours, 24 hours, and 50 hours later. The image-processing method is described in the text. Appropriate image manipulation [see (d)] removes most whole-body background from the doubly injected mouse (center) and reveals specific radioactivity in the MH-15 teratocarcinoma.

seen; but we believe that the difficulties of preparation will be minor in comparison with the advantages gained.

Details of the experimental procedure were as follows: The MH-15 teratocarcinoma cell line, derived from a BALB/c teratocarcinoma by Solter and Knowles (*9*), and the P3-X63-Ag8 BALB/c myeloma cell line (*8*) were grown in Dulbecco's modified Eagle's medium supplemented with 2 m*M* glutamine and 15 percent heat-inactivated fetal bovine serum. Monoclonal antibody against stage-specific embryonic antigen 1 (SSEA-1) (*6, 9*) is an immunoglobulin M (IgM) as is the nonspecific antibody produced by ABPC-22, a BALB/c myeloma isolated by McKean *et al.* (*10*). Both antibodies were purified from the ascitic fluid of hybridoma- or myeloma-bearing BALB/c mice by collecting the void volume after gel exclusion chromatography of ascitic fluid on Sephadex G-200; direct sequence studies (*11*) showed that the monoclonal antibody from ABPC-22 is 85 to 95 percent pure after this procedure. That the void volumes consist almost exclusively of IgM was confirmed by electrophoresis. We cannot exclude the possibility that either monoclonal antibody was contaminated by a small amount of general mouse IgM. Antibodies were iodinated (*12, 13*) and unbound iodine was removed by gel exclusion chromatography on Sephadex G-25 in Dulbecco's phosphate-buffered saline.

Scintigraphic detection of ^{131}I in the ^{123}I channel was about 24 percent; there was negligible detection of ^{123}I in the ^{131}I channel. Environmental background (a constant per channel) was determined and subtracted from the raw image in each channel. Subsequently, by using the ^{131}I-injected mouse (specific antibody only), the ratio of counts in an appropriate area of the "^{123}I image" to the counts in the corresponding area of the ^{131}I image was determined. The entire ^{131}I image of all three mice was multiplied by this ratio ($^{123}I/^{131}I$) to generate a "false" ^{123}I image caused by ^{131}I radiation detected in the ^{123}I channel. This "false" ^{123}I image was then subtracted from the ^{123}I image to yield a corrected, "true" ^{123}I image. Finally, an appropriate multiple of the corrected ^{123}I image was subtracted from the ^{131}I image. The correct multiple was determined by assessing, in the doubly injected mouse, the ratio of ^{131}I to "true" ^{123}I in a body area containing no tumor or by successive approximation of the value until the known nontumor area (the majority of the animal's image) disappeared. The correct multiple varied as the experiment proceeded because of the different decay rates of the two radioisotopes. Similar methods have been used by others (*2, 14*). The accuracy of our data manipulations is easily confirmed by comparing the images of those mice injected with a single isotope to the image of the doubly injected mouse.

Fig. 2. A single mouse bearing both a P3-X63-Ag8 myeloma and an MH-15 teratocarcinoma was injected with ^{131}I-labeled antiserum to SSEA 1 as described in the legend to Fig. 1, except that Lugol's solution was administered as in Table 1. Five days after injection, the mouse was imaged with the ^{131}I channel only. After imaging, organs were removed, weighed, and counted as in Table 1. The ratio of MH-15 radioactivity to P3-X63-Ag8 radioactivity was 26:1, about the same as for tumor to liver (22:1) and tumor to spleen (30:1); the MH-15 to muscle ratio was 195:1.

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References and Notes

1. D. Pressman and G. Keighley, *J. Immunol.* **59**, 141 (1948); D. Pressman, in *Handbook of Cancer Immunology*, H. Waters, Ed. (Garland STPM, New York, 1978), vol. 5, pp. 29–50; C. McGaughey, *Oncology* **29**, 302 (1974); P. B. Hoffer, K. Lathrop, C. Beckerman, V. S. Fang, S. Refetoff, *J. Nucl. Med.* **15**, 323 (1974).
2. D. M. Goldenberg, F. DeLand, E. Kim, S. Bennett, J. Primus, J. R. vanNagell, Jr., N. Estes, P. DeSimone, P. Rayburn, *New Engl. J. Med.* **298**, 1384 (1978).
3. P. Belitsky, T. Ghose, J. Aquino, S. T. Norvell, H. A. Blair, *J. Nucl. Med.* **19**, 427 (1978); P. Belitsky, T. Ghose, J. Aquino, J. Tai, A. S. MacDonald, *Radiology* **126**, 515 (1978).
4. J. Martinis and C. M. Croce, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 2320 (1978).
→ H. Koprowski, Z. Steplewski, D. Herlyn, M. Herlyn, *ibid.*, p. 3405.
6. B. B. Knowles, D. P. Aden, D. Solter, in *Lymphocyte Hybridomas*, F. Melchers, M. Potter, N. L. Warner, Eds. (Springer-Verlag, New York, 1978), pp. 51–53.
7. R. H. Kennett and F. Gilbert, *Science* **203**, 1120 (1979).
→ G. Köhler and C. Milstein, *Nature (London)* **256**, 495 (1975).
9. D. Solter and B. B. Knowles, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 5565 (1978).
→ D. J. McKean, M. Bell, M. Potter, *ibid.*, p. 3913.
11. D. J. McKean, unpublished data.
12. P. J. Fraker and J. C. Speck, Jr., *Biochem. Biophys. Res. Commun.* **80**, 849 (1978).
13. The ^{131}I was purchased (as NaI) from New England Nuclear; ^{123}I (also as NaI) was purchased from the Crocker Research Laboratory, University of California at Berkeley.

14. R. M. Beihn, Jr., R. Damron, T. Hafner, *J. Nucl. Med.* **15**, 371 (1974).
15. We thank D. J. McKean (Mayo Clinic, Rochester, Minn.) for generous gifts of antibody and ascites fluid produced by ABPC-22; L. Gummerman (Presbyterian-University Hospital, Pittsburgh, Pa.) for advice and criticism; and B. Carson and C. Mazzetti (Presbyterian-University Hospital, Pittsburgh, Pa.), J. Reiland (VA Medical Center, Oakland, Pittsburgh, Pa.), and S. Boggs (School of Medicine, University of Pittsburgh) for technical assistance. This work was supported by research funds from the Veterans Administration; the Division of Urological Surgery and the Division of Nuclear Medicine of the Department of Radiology, School of Medicine, University of Pittsburgh; PHS grants CA 10815 and CA 21069 from the National Cancer Institute and HD 12487 from the National Institute of Child Health and Human Development and grant PCM 78-16177 from the National Science Foundation.

23 March 1979; revised 14 May 1979

Activation of the Supplementary Motor Area During Voluntary Movement in Man Suggests It Works as a Supramotor Area

Abstract. *Measurements of cerebral blood flow in man revealed that complex voluntary movements are associated with a blood flow increase in the supplementary motor area of the brain. This increase is additional to and similar in magnitude to the Rolandic sensorimotor area activation that occurs during all kinds of movement. When subjects counted silently there was no activation of any focal cortical area in the brain; when they counted aloud there was a marked increase in activity in the supplementary motor area. These results are consistent with the hypothesis that the supplementary motor area plays a major role in the initiation and control of at least some kinds of voluntary movement in man and is, therefore, a motor center of a higher order than the primary Rolandic areas.*

Cortical stimulation studies (*1*) have located the supplementary motor area (SMA) in man and animals. It is immediately anterior to the primary sensorimotor area for the foot and leg on the medial aspect of both cerebral hemispheres. But its role in voluntary and other movements has still not been clarified some 30 years after its original description. Unilateral ablation of this area for intractable focal epilepsy in man results in a transient akinesia—global at first, with speechlessness, then contralateral to the ablation. Recovery is nearly complete after a few weeks, except for a permanent inability to perform rapid alternating movements with the hands (*2*). It was therefore hypothesized that the SMA might initiate and sustain voluntary motor activity and that other areas, particularly the contralateral SMA, could almost completely compensate for the effects of unilateral ablation (*2*).

In normal brain cortex, an increase in function in a given area produces an increase in the metabolism of its neuronal and glial cell populations, with a concomitant increase in the cerebral blood flow (CBF) to that area (*3*). Measurement of regional CBF thus permits investigation of regional cortical activation: The CBF of many discrete areas of one cerebral hemisphere can be mapped after a bolus injection of a small dose of ^{133}Xe into the internal carotid artery. The clearance of the isotope from the labeled hemisphere is measured externally by multiple scintillation detectors and the flow under each detector is computed by using the initial slope method (*4*). The use of a high-resolution multidetector scintillation camera with 254 detectors has demonstrated that specific patterns of increase in regional CBF can be elicited in normal subjects by various external stimuli or brain functions (*4*). In particular, CBF increases of up to 40 percent occur in the upper premotor region of both hemispheres during simple speech such as counting aloud (*5*) or complex (planned) sequential movements of the fingers (*6*). Simple saccadic eye movements in response to a rapidly moving target are associated with a small but definite increase of CBF in this area (*7*); more complex eye movements, such as occur in looking at pictures or reading silently, are accompanied by a slightly higher flow increase of about 15 percent (*8*). Conversely, during a sustained isometric contraction of the fingers there is only a moderate focal CBF increase in the mesial premotor region, an increase that cannot be distinguished from the diffuse increase of the hemispheric blood flow. Also, during forceful repetitive finger flexions (against a spring), no activation in the mesial premotor region occurs despite the more strenuous muscular work involved compared to the planned motor sequence test (*6*). In contrast, simple repetitive flexion of all fingers without external resistance usually elicits an obvious increase of CBF in this area (*9*).

Thus it was suggested (*6*) that the mesial premotor cortex helps control the motoric subroutines needed for skilled movements and, in view of the size of the area of activation and its localization at the upper border of the hemisphere, it was hypothesized (*6*) that the regions in which these CBF increases occur correspond to or at least include the SMA.

In this report we demonstrate that complex sequential voluntary movements activate the SMA and the appropriate sensorimotor (Rolandic) areas, without obvious somatotopy within the SMA.

We used a 254-detector gamma-ray camera to study the regional CBF correlates of the premotor activations associated with voluntary movements in five patients who were subjected to carotid angiography for focal epileptic seizures and shown to be free of brain lesion. With this camera, CBF can be recorded in 254 small adjacent cortical areas, each about 1 cm^2 (*4*).

The detectors were positioned above the head of the patient in a plane facing the vertex of the skull, with the midline of the collimator array in alignment with the midline of the brain. (Measurements made by the detectors positioned over the nonlabeled hemisphere in this position were excluded from the results.) Two to five consecutive regional CBF measurements were made in each patient (a total of 25 determinations). Measurements were made under a number of experimental conditions. Three patients lay motionless with eyes closed and ears plugged; four performed static foot contraction (pushing the foot contralateral to the labeled hemisphere against a continuous resistance); five performed sequential foot movements for 45 seconds (moving the toes once downward, twice upward, three times to the right, four times to the left, and then repeating this sequence); four performed complex sequential finger movements (*6*); one performed repetitive saccadic horizontal eye movements; three counted aloud from 1 to 20; two made sequential mouth movements (alternately baring the teeth and protruding the lips); and three counted silently from 1 to 20 several times, without moving the lips or tongue.

Contralateral sustained foot contraction resulted in all cases in an increase in CBF of 17 to 28 percent (mean, 24 percent) in an area 2 to 3 cm in diameter in the cortex close to the midline (Fig. 1A), an area that corresponds to the sensorimotor area for the foot. The complex foot movement sequence was accompanied by an even higher CBF increase of 22 to 38 percent (mean, 29.5 percent) in this region, with the appearance of a second small focus of increased CBF, about 2 cm in diameter, just anterior and slightly medial to the sensorimotor foot area (Fig. 1B)—corresponding exactly to

0036-8075/79/1116-0847$00.50/0