Advances in the Use of Visual Imaging: Techniques in Mental Illness

By WILLIAM E. BUNNEY, JR., M.D., BLYNN GARLAND and MONTE S. BUCHSBAUM, M.D.

The introduction of four new computerized techniques in medicine has provided scientists with the ability to directly observe and measure the activity of the living human brain as it responds to various stimuli. Visual imaging techniques may provide the necessary tools for the understanding of many central nervous system diseases including that of mental illness. Currently, psychiatry is one of the fields at the leading edge in applying visual imaging techniques to study brain function. Metabolic measures of regional brain activity may provide clues to the identification of relevant brain abnormalities not provided by indirect analysis of whole brain function, identify individuals vulnerable to mental illness, and help in the development of more specific and effective treatments for psychiatric illness.

The measurement of brain activity has been a challenge to scientists for many years. The progression from electroencephalography (EEG) to cerebral blood flow studies, nuclear magnetic resonance (NMR) and positron emission tomography (PET scan) has significantly improved the physician's understanding of brain function. Another brain imaging technique, computerized axial tomography (CAT scan) is discussed elsewhere in this issue (Weinberger and Wyatt).

Historically, one of the earliest methods used to measure brain activity was the electroencephalogram (EEG). It is a noninvasive technique which allows for the measurement of spontaneous patterns of electrical activity as well as cortical activity in response to specific stimuli. One of the major limitations in the use of EEG in psychiatric research has been the difficulty in quantifying large amounts of data recorded from multiple electrode sites. The development of spectral analysis on small and inexpensive laboratory computers brought quantitation to the clinical level, but the high volume of numerical results made neuroanatomical correlations difficult to see. Recent developments have introduced techniques for two-dimensional mapping of the electrical activity of the brain. This method allows for color-coded EEG activity maps and is presented visually on a representation of the cortical surface. Thus far, EEG topographic analysis appears to be compatible with results from other brain activity studies.

Before the advent of current visual imaging techniques it was necessary to rely on conventional radiography which used x-ray opaque dyes (cerebral angiography) or air to replace ventricular fluid (pneumoencephalography). Although these methods yielded interesting data, the detailed study of brain function was difficult because structures often overlapped and had similar densities. In 1948, Kety et al. ingeniously used a combination of nitrous oxide (a freely diffusible tracer) and arteriovenous measurements to obtain the first data on total cerebral blood flow and metabolism in the living human brain. While Kety and co-workers found no differences between patients with schizophrenia and other subjects, they suggested the possible future value of a regional brain approach. Kety's recognition of the importance of cerebral metabolism and suggestion of the importance of regional approaches provided the impetus for the brain...
imaging techniques used today.

The next major development, almost two decades later, was the replacement of nitrous oxide with radioactive tracers (e.g., $^{133}$Xenon) which produce a two-dimensional view of the brain and enable investigators to observe and measure cerebral blood flow using external detectors and cathode-ray-tube images. With this technique, Ingvar and Risberg were able to demonstrate for the first time regional differences between patients with schizophrenia and normal controls as well as possible changes in cerebral blood flow in various experimental conditions.\(^7\)

The most recent technical advancement to evolve is the PET scan (positron emission tomography), which has made possible the regional approach suggested by Kety. A brilliant discovery was made by Sokoloff et al.\(^1\) who introduced methods for quantifying cerebral glucose metabolism. Combined with positron tomography, this technique provides the means for three-dimensional functional mapping of the living human brain.

This article will review the latest advances in four visual imaging techniques including $^{133}$Xe blood flow techniques, EEG and evoked potential topography, nuclear magnetic resonance (NMR) and positron emission tomography (PET scan).

**ELECTROPHYSIOLOGICAL STUDIES**

Electroencephalography (EEG) is a technique which measures brain electrical activity by recording electrical impulses from electrodes placed on the scalp. This methodology can be used to assess spontaneous activity as well as responses to specific stimuli. The EEG can be divided into four major rhythms. The alpha rhythm is a 10 cycle/second pattern which frequently appears in the posterior parietal and occipital regions of the brain in normal individuals resting with their eyes closed. This rhythm is blocked when the eyes open. Delta and theta rhythms which are slower than alpha are associated with drowsiness. Finally, the fast beta rhythm is associated with mental activity. The proportion of each of these brain rhythms is very sensitive to psychoactive medication.\(^6\) Delta rhythms (associated with drowsiness) have been reported to be more prevalent in the frontal lobes of drug-free schizophrenics as compared to normal controls consistent with decreased blood flow in the frontal cortex of schizophrenics.\(^7\)

NUCLEAR MAGNETIC RESONANCE IMAGING (NMR)

Nuclear magnetic resonance (NMR) is based on the reception of radio frequencies emitted by nuclei of different elements in the brain following application of a magnetic field.\(^10\) In 1952, Drs. Felix Bloch and Edward Purcell won the Nobel prize for developing NMR spectroscopy techniques. The development of computer-coded visual displays of NMR data almost three decades later has revived interest in this potentially powerful diagnostic tool. In a recent review, Pykett described the NMR technique.\(^12\) Atomic nuclei generate small magnetic fields dependent on their spin properties. The nonzero spin nuclei are made up of those nuclei having odd numbers of protons or neutrons. The NMR technique is capable of detecting the magnetic behavior of the nuclei by measuring the net effect of all the magnetic moments of the nuclei in a sample of material. Early clinical results at Massachusetts General Hospital suggest that NMR is good at detecting dead tissue, local anemia caused by mechanical obstruction of the blood supply, malignancies and degenerative diseases. The soft-tissue analysis has been reported to be superior to that of the x-ray techniques. A limiting factor for medical practice is that some parts of the body appear to be more amenable to NMR analysis. For example, the head can be kept relatively still while the beating heart may require special high-speed imaging techniques or synchronization of the data over a series of cardiac cycles. Although no psychiatric studies have been completed, this technique potentially allows for the measurement of cell energy metabolism and NMR-sensitive labeled pharmaceuticals. However, the distributions of NMR-sensitive nuclei other than protons in the water are in low concentrations, and current technology has allowed for high resolution only of gray and white matter of brain structures. The potential of the NMR as a technique to identify specific biological markers has yet to be investigated, but it conceptually appears that it might be valuable in the identification of functional cell nuclei.

BLOOD FLOW TECHNIQUES

Cerebral blood flow is closely related to cerebral metabolism (oxygen consumption and glucose use). Regional cerebral blood flow can be studied with the $^{133}$Xenon washout techniques. The isotope is injected into the internal carotid artery or breathed as a mixture with

continued on page 424
One 30-mg capsule, h.s.—usual adult dosage.
One 15-mg capsule, h.s.—recommended initial dosage for elderly and/or debilitated patients.

INDICATIONS AND USAGE: Restoril® (temazepam) is indicated for the relief of insomnia characterized with complaints of difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Since insomnia is often transient and intermittent, the prolonged administration of Restoril is generally not necessary or recommended. Restoril has been employed for sleep maintenance for up to 35 consecutive nights of drug administration in sleep laboratory studies.

The possibility that the insomnia may be related to a condition for which there is more specific treatment should be considered.

CONTRAINDICATIONS: Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Also, ingestion of therapeutic doses of benzodiazepine hypnotics during the last weeks of pregnancy has resulted in nonselective CNS depression. Restoril is contraindicated in pregnant women. Consider a possibility of pregnancy when instituting therapy or whether patient intends to become pregnant.

WARNINGS: Patients receiving Restoril (temazepam) should be cautioned about possible combined effects with alcohol and other CNS depressants.

PRECAUTIONS: In elderly and/or debilitated patients, it is recommended that initial dosage be limited to 15 mg. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary. If Restoril is to be combined with other drugs having known hypnotic properties or CNS-depressant effects, due consideration should be given to potential additive effects.

Information for Patients: Patients receiving Restoril should be cautioned about possible combined effects with alcohol and other CNS depressants. Patients should be cautioned not to operate machinery or drive a motor vehicle. They should be advised of the possibility of disturbed nocturnal sleep for the first or second night after discontinuing the drug.

Laboratory Tests: The usual precautions should be observed in patients with impaired renal or hepatic function. Abnormal liver function tests as well as blood dyscrasias have been reported with benzodiazepines.

Pregnancy: Pregnancy Category X. See Contraindications. Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS: The most common adverse reactions were drowsiness, dizziness and lethargy. Other side effects include confusion, euphoria and relaxed feeling. Less commonly reported were weakness, anorexia and diarrhea. Rarely reported were tremor, ataxia, lack of concentration, loss of equilibrium, falling and palpitations. And rarely reported were hallucinations, horizontal nystagmus and paradoxical reactions, including excitement, stimulation and hyperactivity.

Restoril is a controlled substance in Schedule IV. Caution must be exercised in addiction-prone individuals or those who might increase dosage.

DOSEAGE AND ADMINISTRATION: Adults: 30 mg usual dosage before retiring, 15 mg may suffice in some. Elderly and/or debilitated; 15 mg recommended initially until individual response is determined.

SUPPLIED: Restoril (temazepam) capsules—15 mg maroon and pink, imprinted “RESTORIL 15 mg”; 30 mg, maroon and blue, imprinted “RESTORIL 30 mg”. Packages of 100, 500 and ControlPak® packages of 25 capsules (continuous resalable household roll of sealed blisters) (RES-22/11/1/81)

Before prescribing, see package insert for full product information.
was a marked increase in the premotor and frontal regions. However, when the actual movement took place, the cerebral blood flow pattern markedly changed to a localized increase in the hand area of the primary motor cortex. Thus, brain areas associated with the planning and organization of behavior and revealing task-related blood flow changes are the same ones with low flow in patients with schizophrenia.

Studies of patients with depression have reported a decrease in right hemisphere blood flow. Additional studies have reported decreased blood flow in manics and depressives.

**PET SCAN TECHNIQUES**

The exciting development of positron emission tomography (PET scan) has allowed scientists to measure the functional activity of the living human brain. For the first time it is possible to obtain three-dimensional colored mappings of the metabolic activity of brain regions during specific psychological states or tasks. The methodology is based on a triad of technical advances. A mathematical model, originally developed by Sokoloff and associates in 1977, allows quantification of regional brain glucose use from a glucose analogue autoradiography technique. The development of small but highly sensitive crystal detection and coincidence counting electronics, together with the mathematical reconstruction techniques similar to those used for CT, allows quantitative images to be generated. Glucose metabolism is an indicator of brain work since cerebral tissues under normal circumstances derive most of their energy from glucose. The amount of glucose metabolized in a specific structure at a certain point in time is related to the amount of cell firing and repolarization activity in that neuronal structure. Preliminary work in animals suggests that glucose metabolism is sensitive to changes in functional activity including sleep, electrical stimulation, olfactory stimuli, circadian rhythms, visual and auditory activity, stress and the administration of various pharmacological agents. Furthermore, these findings are consistent with other measures of brain activity such as blood flow studies and EEG recordings.

PET scan technology is a fascinating combination of several scientific disciplines including physics, computer science, neurology, radiology, pharmacology, biochemistry, psychiatry, and mathematics. Basically, PET scan methodology involves the intravenous administration of a neutron-deficient isotope which contains a proton. Because of the rapid decay of most common elements (oxygen-15, two minutes; nitrogen-13, ten minutes; carbon-11, 20 minutes), fluorine-18 has been chosen as the most valuable label as it has a half-life of 110 minutes and therefore allows for longer periods of analysis. The proton decays to a neutron and a positron is emitted. Initially, the positron is at a very high energy level but interacts with an electron in a very short distance and spontaneously annihilates. Energy is then released in the form of two high energy photons (or gamma rays) which travel in opposite directions (180 degrees apart). Multiple radiation detectors which are arranged in a circle are activated only when both photons hit detectors 180 degrees apart simultaneously. This technique accurately determines the line segment in which the isotope resided. The data are then analyzed by a computer which constructs three-dimensional color-coded slice images of brain structures demonstrating a quantitative display of biochemical activity of glucose use. Currently, in addition to deoxyglucose, scientists are considering labeling compounds which can be used to study neuroreceptors (i.e., protein synthesizer, and labeled psychoactive agents such as neuroleptics and benzodiazepines). Some of these agents include $^{18}$F-labeled haloperidol, $^{15}$F-labeled spiroperidol, $^{11}$C-labeled pimozide, and $^{11}$C-labeled flunitrazepam.

More than 500 patients and normal volunteers have been studied using PET scan techniques in seven operating centers. Thus far, evidence suggests that it is possible to study various disease states and their effects on brain function. In a series of studies in man, glucose metabolism was shown to be altered in response to auditory, verbal, visual and shock stimuli, and during periods of aphasia. Recent findings using PET scan techniques comparing schizophrenics to normals have been very promising. In a longitudinal study, Farkas et al. studied a 45-year-old patient with a history of schizophrenia since the age of 16. Although the patient had never had neuroleptic medication before the scan, there was still a 40% decrease in frontal cortex glucose use as compared to controls. When the patient was treated with phenothiazines, there was an apparent return to normal glucose utilization levels.

In our recent report, local cerebral glucose use was measured with $^{18}$F-labeled 2-fluorodeoxyglucose (FDG) in eight unmedicated schizophrenic patients and six age-matched normal volunteers. Subjects sat resting in a quiet darkened room with eyes closed after the injection of an isotope-labeled glucose analogue. Following uptake, we obtained seven to eight horizontal brain scans parallel to a line connecting the outer canthus of the eye with the external auditory meatus. Patients with schizophrenia.
showed relatively lower glucose use in frontal than occipital cortex than normal controls. These results are consistent with previous blood flow studies which demonstrated decreased blood flow in schizophrenic patients during similar experimental (rest-eyes closed) conditions. Diminished pain responses in schizophrenics and affectively ill patients were also demonstrated in both PET scan and blood flow studies, again illustrating a consistent relationship between the two techniques.

Although the PET scan technique is in its early developmental stages, there appears to be promise in the future that it will have a major impact on the understanding and treatment of mental illness. In fact, there is some hope that PET scan results will have the potential of serving as trait- or state-markers of mental illness and will someday help in the identification of high-risk individuals. For example, it may be possible that abnormal metabolic brain functioning will alert the physician to the potential of developing mental illness.

REFERENCES