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YEAR BOOK OF NUCLEAR MEDICINE® 1989

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The Year Book of NUCLEAR MEDICINE®

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Journals Represented

Year Book Medical Publishers subscribes to and surveys almost 700 U.S. and foreign medical and allied health journals. From these journals, the editors select the articles to be abstracted. Journals represented in this YEAR BOOK are listed below.

American Heart Journal
American Journal of Cardiology
American Journal of Diseases of Children
American Journal of Emergency Medicine
American Journal of Medicine
American Journal of Neuroradiology
American Journal of Roentgenology
Anesthesiology
Annales Chirurgiae et Gynaecologiae
Annals of Internal Medicine
Annals of Neurology
Annals of Nuclear Medicine
Annals of Surgery
Applied Radiation and Isotopes- Part A
Archives of Internal Medicine
Archives of Surgery
British Heart Journal
British Journal of Radiology
Cancer
Cancer Research
Chest
Circulation
Circulation Research
Clinical Nuclear Medicine
Clinical Radiology
Diseases of the Colon and Rectum
European Heart Journal
Health Physics
Hypertension
Injury
International Journal of Cardiology
Investigative Radiology
Journal of the American College of Cardiology
Journal of the American Medical Association
Journal of the Applied Physiology: Respiratory, Environmental and Exercise Physiology
Journal of Bone and Joint Surgery (American Vol.)
Journal of Clinical Investigation
Journal of Computer Assisted Tomography
Journal of Neurology, Neurosurgery and Psychiatry
Journal of Neurosurgery
Journal of Nuclear Medicine
Journal of Pediatric Gastroenterology and Nutrition
Journal of Thoracic Imaging
Journal of Thoracic and Cardiovascular Surgery
Journal of Trauma
Journal of Vascular Surgery
Lancet

Life Sciences
Lung
Magnetic Resonance Imaging
Magnetic Resonance in Medicine
Neurology
New England Journal of Medicine
Nuclear Medicine and Biology - Part B
Nuclear Medicine Communications
Nuclear Medicine
Proceedings of the National Academy of Sciences
Radiology
Scandinavian Journal of Clinical Laboratory Investigation
Seminars in Nuclear Medicine
Skeletal Radiology
Thorax
Western Journal of Medicine
Journal of Cerebral Blood Flow and Metabolism
CRC Critical Reviews in Biochemistry

Standardized Abbreviations

A large number of articles this year deal with computed tomography, diethylenetriaminepentaacetic acid, magnetic resonance imaging, nuclear magnetic resonance, positron emission tomography, and single photon emission tomography. We have chosen not to spell out the names of these techniques in full each time the abbreviations appear in a new article. These are designated CT, DTPA, MRI (or MR), NMR (or NMRI), PET, and SPECT, respectively, throughout the book.

Introduction

On Singles and Pairs

This year's Quinn Memorial Essay by Drs. Alavi and Kung is on the subject of single-photon-emitter-labeled receptor binding agents. In the world of neuroreceptor binding, it was long assumed that a positron emitter such as fluorine 18 or carbon 11 would be a necessary ingredient of any clinically useful receptor binding agent. This assumption was based on the fact that most neurotransmitters and analogues are low-molecular-weight compounds that would not tolerate tagging with such heavy labels as iodine 123, technetium 99m, or indium 111. As a result of the pioneering work by the University of Pennsylvania group and others, it is now obvious that many receptors can be identified, and perhaps quantified, using single-photon-emitter-labeled compounds. This may significantly reduce the expense involved in studying the distribution of at least some of these receptors. Equally important, it will expand the number of medical centers having the capability of carrying out such investigations. It may come as a shock to some of the more devoted poker players in our readership, but at least when it comes to radiotracers there are times when a good singleton beats a pair. This is especially true in games where the ante for a Cyclotron/PET facility is in the multimillion-dollar range while the head SPECT imaging units are an order of magnitude less expensive.

I was embarrassed this year to receive a letter from a good friend who felt we may have engaged in some camera "bashing." This started off as an innocent comment by one of the Associate Editors that unfortunately was subject to misinterpretation. While an apology is in order and has been given, I am afraid that the YEAR BOOK comments will always be prone to such inadvertent double meanings. The Editors strive, like Horton the Elephant, to say what we mean and mean what we say. Unfortunately, as I have pointed out in previous introductory remarks, the production schedule for the YEAR BOOK does not allow for review and editing of the comments. Therefore, not only do typographical errors occasionally appear but, perhaps more embarrassing, the comments sometimes read with a different slant than was intended. My usual custom to prevent such errors in other written work is to prepare a manuscript and then bury it in my desk for 6 weeks. I then retrieve it and have an opportunity to read it fresh. Given my short memory span, I am often amused by the erroneous or unintended interpretations I can make from that which I myself have written.

While on the subject of errors, there is another to which I must also plead occasional guilt. That is the use of malapropisms, misspoken or, in this situation, miswritten words. Jack Rosenthal, in his guest editorial on language in the August 28 issue of *New York Times Magazine*, reminds us of Yogi Berra's classic malapropism, "It's deja vu all over again." Mr. Rosenthal goes on to discuss another classic group of errors familiar to anybody who has ever dictated a radiologic or nuclear medicine report. These are spoonerisms or mispronunciations. They include such classics as globular infiltration (glomerular filtration) and marineland heart

(Marine-Lenart). While spoonerisms have frequently been a source of local humor in most hospitals, I know of no previous effort to catalog and preserve some of the finer examples. Therefore I invite all the readers of the YEAR BOOK to participate in the first (and perhaps last) effort to collect the 10 greatest nuclear medicine spoonerisms of all time. Since the financial rewards to the Editors of the YEAR BOOK are relatively modest, cash awards are out of the question. However, Year Book Medical Publishers will provide the contributor of the winning spoonerism with a complimentary copy of any YEAR BOOK. In addition, I promise that the contributors of outstanding spoonerisms will be acknowledged appropriately. There will also be a book award for the winner in the Resident/Fellow category. I promise that the judging will be fair and square, although out of concern for future professional activities, the judges will not be blinded. (That is neither a malapropism nor a spoonerism; it's not even a bad pun!)

I am grateful to Dr. Paul Gagliardi for his continued help in spotting significant articles, to Harriet Comen for her secretarial services that included keeping me and the Associate Editors on schedule, and the staff of YEAR BOOK for their continued support.

Paul B. Hoffer, M.D.

Imaging of the Brain With SPECT: Is It Coming of Age?

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Historical Background

In 1963, Kuhl and Edwards published the first report on emission computed tomography (ECT) (1). These investigators built a tomographic scanner that performed linear scans at discrete angles around human subjects and processed the data with linear superposition of back projections. Kuhl's work was the first example of a transaxial reconstruction of radionuclide distribution. The group later improved the reconstruction algorithms by using an orthogonal tangent iterative correction technique instead of linear superposition of back projections (2–3). At the University of Pennsylvania, Kuhl et al. designed and constructed 3 tomographic machines from the early 1960s to mid-1970s (3–5). These instruments were extensively used clinically in a variety of neurological disorders (6), with ^{99m}Tc pertechnetate being the principal radionuclide. These studies enabled this group to detect breakdown in the intracranial lesions with higher sensitivity and also to define them better anatomically than conventional techniques (7). This approach was especially useful in the detection of abnormalities in the base of the skull and posterior fossa.

During the early 1970s, with the advances made in the development of reconstruction algorithms, it became possible to obtain images in which the density was linearly related to radionuclide concentration within the examined section (2). Therefore, a digital representation of an image can be quantitatively related to radionuclide concentration. This technique was used to quantify local cerebral blood volume after the administration of ^{99m}Tc-tagged red blood cells (8,9). A blood sample was taken during the scan and the concentration of activity in red blood cells and in plasma measured. The digitally reconstructed image and the measured concentration of radioactivity in the blood were used to determine local cerebral blood volume in milliliters per deciliter of tissue. The reliability of this technique was examined in baboons, and a good correlation was demonstrated between the measured values in vitro and the data obtained by ECT (8). Baboons were also used to determine the relationship between the local cerebral blood volume and both $PaCO_2$ and mean arterial blood pressure. These results were found to be in good agreement with other data reported in the literature.

Emergence of X-Ray Computed Tomography and Positron Emission Tomography

In 1973, Hounsfield introduced transmission (x-ray) computed tomography (XCT) using x-ray beams (10), making excellent anatomical delineation of the brain possible. It was soon shown that by the intravenous

administration of water-soluble iodinated contrast media used for pyelography and angiography, many of the focal lesions of the brain could be demonstrated more distinctly (11). An excellent correlation was noted between the enhancement of focal lesions and their demonstration on radionuclide studies (7). Therefore, it became apparent that the lesions demonstrable by radionuclide studies could be readily shown by contrast-enhanced XCT scans. The major advantage of XCT is its capacity to show the anatomy of the brain and the abnormalities with extremely high resolution. Although the impact of this modality was not fully realized initially, within a short period of time this technique was accepted as the study of choice in the evaluation of neurological disorders. The introduction of this technique resulted in a dramatic decline in the number of radionuclide studies of the brain performed in almost every institution.

To utilize fully the capabilities of ECT, investigators from the University of Pennsylvania further evaluated the use of regional blood volume measurement in a variety of neurologic disorders. In a study of patients with head trauma, it was soon realized that patients with intracerebral hematoma demonstrate areas of hyperemia surrounding the site of hemorrhage (12). This may explain the symptoms and signs of their presentation and could be used to guide the management of these patients.

An attempt was made to measure regional cerebral blood flow (rCBF) and perfusion using diffusible indicators in conjunction with ECT. One such successful application was accomplished by the use of ^{123}I-iodoantipyrine (3). This agent clearly delineates areas of decreased perfusion secondary to vascular occlusion. After injection this agent is significantly cleared by the brain in 1 circulatory passage. During the first minute or 2 after injection it remains locally deposited in the brain in proportion to rCBF, with the areas of decreased perfusion appearing devoid of activity while the rest of the brain has considerable tracer uptake.

With these developments it became apparent that the role of nuclear medicine procedures was to be redefined to show regional cerebral function and metabolism rather than anatomical delineation. Unfortunately, the number of radiopharmaceuticals available to perform this type of work was limited at that time. Because of this, investigators from institutions with access to a cyclotron explored the possibility of using positron emitters with PET to better outline the function and anatomy of the brain.

One of the major breakthroughs in the 1970s was the development of the C-14 deoxyglucose technique by Sokoloff et al. (13). This autoradiographic technique made it possible to measure the rates of glucose metabolism in specific discrete regions of the brain in different states of activity. The extension of this method to humans required labeling deoxyglucose with a gamma emitting radionuclide. With the successful synthesis of (F-18) fluorodeoxyglucose (FDG), the requirements for a suitable radiopharmaceutical and the determination of regional cerebral glucose metabolism were fulfilled (14).

The FDG technique of measuring regional cerebral metabolic rate for

glucose (rCMRglu) has been well accepted and widely used by many institutions around the world. A large number of studies have been carried out in normal volunteers and patients with a variety of CNS disorders (15). Some important and interesting findings have been revealed following sensory, motor, visual, and auditory stimulations. Functional imaging with FDG in certain neurologic disorders has dramatically improved our understanding of their underlying pathophysiologic phenomena. Some abnormalities detected on the PET images have no corresponding changes on x-ray computed tomograms.

Imaging Regional Cerebral Blood Flow With SPECT

Unfortunately, imaging regional cerebral blood flow with SPECT and investigation of the regional cerebral function and metabolism has been limited to centers with access to on-site cyclotrons and strong radiochemistry support. The unusual success of PET in mapping regional cerebral function and metabolism, and the difficulty in disseminating this technology to centers without a cyclotron, resulted in resurgence of SPECT after almost a decade. I-123-labeled amines introduced in the early 1980s were the first radiotracers to be used to determine regional brain function. I-123-N-Isopropyl-p-iodoamphetamine (IMP) (16) and I-123-N-N,'N,-trimethyl-N'-[2-hydroxyl-3-methyl-5-iodo-benzyl]-1,3 propane diamine (HIPDM) (17) were the 2 radiopharmaceuticals that appeared quite promising for human applications following early investigations in animals. The uptake and distribution of these tracers in the brain appears to be proportional to blood flow (18). Both compounds have been used extensively in man, and their usefulness has been clearly established (19). The recent introduction of Tc-99m-labeled compounds has further improved the ability to acquire high quality functional imaging of the brain with SPECT. The 2 most successful of these compounds (HMPAO and ECD) are investigated for widespread application in a variety of CNS disorders (20). ECD is chemically more stable than HMPAO and at this time appears to be the agent of choice for SPECT imaging of the brain (21).

Flow and metabolism are coupled in most chronic pathologic states and determination of regional flow with SPECT will reveal images similar to those obtained with metabolic tracers utilizing PET (22). However, in certain acute disorders such as cerebrovascular accidents, dissociation occurs between these 2 parameters and determining 1 cannot always predict the other (23). This is the major shortcoming of the flow tracers that are used in isolation without the benefit of compounds which demonstrate regional metabolism. This shortcoming is very difficult to overcome, and we may depend on PET techniques to determine certain metabolic functions in the foreseeable future.

Central Nervous System Dopamine Receptor Imaging

One of the major breakthroughs in medical imaging took place in 1983 when carbon-11-labeled N-methyl spiperone was used to obtain D-2 dopamine images in the brain of a living human being (24). With the

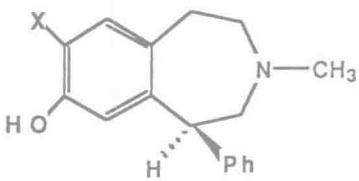
successful implementation of this technique, a new era of investigation of neuropsychiatric disorders was started which will have far-reaching implications. It is generally accepted now that there are 2 major subtypes of dopamine receptors: D-1 and D-2. This designation is based on the ability of agonists and antagonists to discriminate between 2 different distinct dopamine receptors (25–29). These 2 subtypes of dopamine receptors exert synergistic effects on the activity of CNS dopaminergic neurons in rats (30–32). Recently, many reports have suggested that D-1 and D-2 agonists invariably exhibit opposite biochemical effects: D-1 agonists stimulate adenyl cyclase activity, while D-2 agonists inhibit this enzyme's activity. It is clear that these receptor subtypes influence each other, yet they display separate and distinct functions on physiology and biochemistry (32).

Several human CNS diseases, such as schizophrenia, tardive dyskinesia, Parkinson's disease, and Huntington's chorea, involve changes of dopamine receptor density in the brain (33–36). Using in vitro binding techniques with postmortem brain samples from patients with Parkinson's disease, it has been demonstrated that drug naive patients show an increase in D-2 dopamine receptor concentration, but the patients treated with L-DOPA display a normal level of the receptor density. Brain samples of schizophrenic patients consistently show elevated D-2 dopamine receptor concentration. This may be the result of long-term treatment with neuroleptic drugs; however, higher D-2 dopamine receptor density has also been observed in schizophrenic patients with no treatment with neuroleptic medication (36). Recently, quantitative studies by in vivo imaging of schizophrenic patients with [^{11}C]-NMSP (37) and [^{11}C] raclopride (Karolinska's Group) (38–41) reported different results—NMSP showing a higher D-2 dopamine concentration, and raclopride displaying no change in the dopamine density.

SCH-23390 is the first highly selective central D-1 antagonist (42–46). The corresponding Br-(SKF-83566) (47) and I-(SCH-23982 or SKF-103108A) (48–52) compounds have also been shown to have a high specificity for central D-1 dopamine receptors (Table 1).

The Br-compound (SKF R-83556) labeled with ^{86}Br, a positron emitting radionuclide, has been used for PET imaging in a rhesus monkey. It showed the highest concentration in the basal ganglia, with more selectivity in the posterior aspect of the caudate nucleus, the region with high D-1 receptor density (47). Several recent reports have indicated that in

TABLE 1.—Chemical Structures and In Vitro Binding Constants of Benzazepines



X	Compound	Kd(nM)
H	SKF-83692	197
Cl	SCH-23390	0.36
Br	SKF-83566	2.32
I	IBZP, SKF-103108A (or SCH-23982)	0.7

conjunction with PET, [^{11}C]SCH 23390 showed the highest concentration in the basal ganglia area of the human brain (53, 54).

I-123 Labeled CNS D-1 Receptor Imaging

Based on the findings described above, we have prepared a ^{123}I-labled analog of SCH-23390, R-(+)-8-[^{123}I] iodo-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol, [^{123}I]IBZP, (SKF 103108, or SCH 23982) (52). An imaging study of a monkey using [^{123}I]IBZP, specifically for mapping of the CNS D-1 dopamine receptor, demonstrated that the agent localized in the basal ganglia area where D-1 receptor concentration is high. The result is comparable to those reported for N-[^{11}C]methyl-SCH-23390 and the corresponding Br-86 labeled derivative. Results of this monkey imaging study strongly suggest that [^{123}I]IBZP is potentially useful for SPECT imaging of D-1 dopamine receptors in humans.

In our previous report, using [^{125}I]IBZP, the agent showed good localization in the brain after an intravenous injection in rats, with an uptake of 2.7%, 1.2% and 0.8% dose per organ at 2, 15, and 30 minutes post injection, respectively (52). The regional distribution in rat brain, as measured by in vivo autoradiography, displayed a high uptake in the caudate putamen, accumbens nucleus and substantia nigra, regions known to have high concentrations of D-1 dopamine receptors. The uptake ratio of striatum/cerebellum increased with time; at 30 seconds and 2 hours after injection the ratios were 1.1 and 5.3, respectively. The specific uptake regions (as measured by in vivo autoradiography), rich in D-1 dopamine receptors, can be blocked by pretreatment with SCH-23390, a selective D-1 dopamine receptor antagonist (Fig 1).

Immediately after the IV injection of [^{123}I]IBZP the monkey brain showed significant uptake. The brain uptake appeared to reach a maximum at approximately 10 minutes post injection (Fig 2), and the basal ganglia region was apparent at 5 minutes. Since the agent is a very lipid-soluble material (partition coefficient: 1-octanol/buffer = 1156 and 2367, at pH 7.0 and 7.4, respectively), it is likely that IBZP penetrates the blood-brain barrier by a simple diffusion mechanism. The summed images (see Fig 2) demonstrate that the agent is clearly concentrated in the basal ganglia. The washout curve from the brain is shown in Figure 3.

The in vitro dissection experiment using a tissue counting technique showed high uptake in total brain (2.54% per organ, total brain = 57 gm) (Table 2). The ratios of the basal ganglia to cerebellum, and cortex to cerebellum were 3.52 and 1.70, respectively, at 50 minutes post injection. These data are consistent with those reported for rats (52). Other tissue and organ uptake data are presented in Table 2. Liver, muscle, lung, and kidney were the organs with high uptake.

I-123 Labeled CNS D-2 Receptor Imaging

A variety of substituted benzamide derivatives possessing antidopaminergic properties has been reported (55–60). Of these, raclopride and eti-

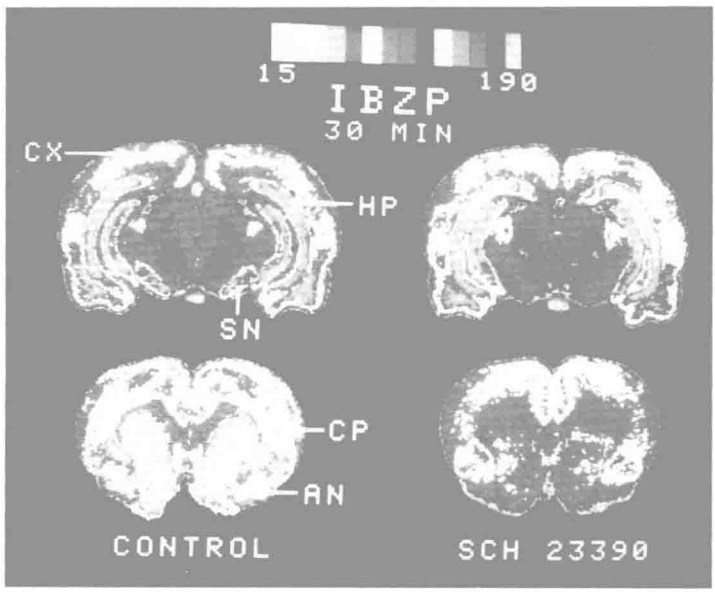


Fig 1.—Autoradiography of [^{125}I]IBZP in normal and SCH-23390-treated rats. The sections from rats pretreated with SCH-23390 display no specific uptake in the striatum area.

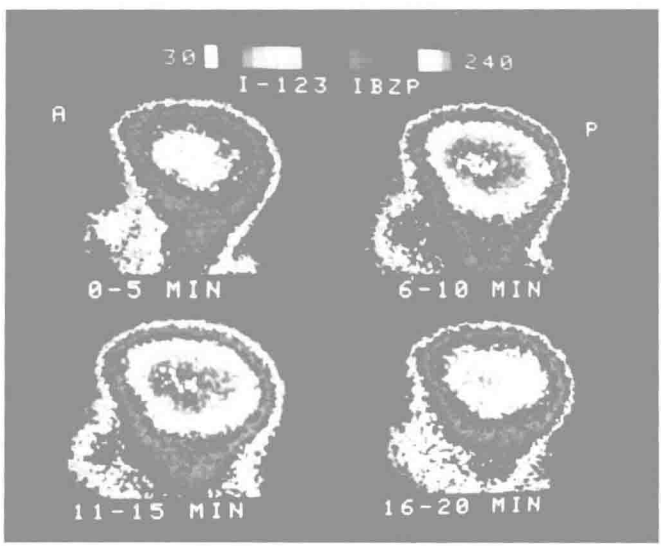


Fig 2.—Lateral images of the monkey's head after an intravenous injection of [^{123}I]IBZP. These represent added images at 1–5 minutes, 6–10 minutes, 11–15 minutes, and 16–20 minutes post injection.