EDITORIAL

Mapping Cerebral Blood Flow

In the past, the announcement of a new radiopharmaceutical was invariably greeted with great enthusiasm and evidence for another great leap in the progress of nuclear medicine. After all, this is the field's chief concern: the application of new tracers to the diagnosis, monitoring and treatment of specific clinical entities. In the golden days of the late 1960's and early 1970's, many new ^{99m}Tc-labeled tracers were developed, often in small laboratories, and clinical applications emerged rapidly thereafter.

More recently, however, some probably healthy skepticism is widely encountered, when a "new tracer" is announced. The main concerns repeatedly expressed can be summarized as follows: is the radiopharmaceutical really new? Does its development add new knowledge to the existing body of data? Is this new knowledge of clinical benefit and can the new tracer be introduced and made widely available within a reasonable short period of time?

Crucial to the success of a new radiopharmaceutical is its marketability. In this context, it is worthwhile to remember that from time of initial conception and data publication to full market introduction as many as seven years may pass by. During this time (rather long for a technologically driven field of medicine) much may have happened that alters the perception of the inventor when he/she analyzed the field and decided that the new tracer had a chance of success. In seven years, major technological advances within the field or within competing modalities may significantly challenge the window of opportunity of the new tracer. For example, a compound developed in the mid 1980's, now reaching market introduction, may not have been designed with the insight that multidetector imaging devices will be routinely available at the time of market registration and maturation. Would ^{99m}Tc-PnAO have developed differently had this technological progress been considered? At least the question deserves to be posed, if only as an intellectual exercise and as a reference in future thinking on the direction for research and development in nuclear medicine.

The costs of developing a new tracer are quite staggering. Between 10 to 20 million dollars can be spent in such a process (a conservative estimate). The multilingual documentation which needs to be prepared for registration purposes world wide is measured today in surrealistic units of weight (tons)! Not infrequently the industry is faced with a market size which is insufficient to support a commercially viable new radiopharmaceutical (the pains with the European registration of dopamine D2 analog labeled with ^{123}I bear witness to this).

We are now approaching the mid 1990's, the turn of the century is only one product cycle away (the magic seven years). Techniques for the measurement or assessment of cerebral blood flow include radioactive tracers, stable tracers and x-ray CT (xenon), magnetic resonance imaging, transcranial Doppler, dynamic CT and infra-red imaging. Any newcomer to the field of radiotracers and this impressive array of techniques will not only have to demonstrate its potential among existing radiopharmaceuticals designed for cerebral blood flow (^{133}Xe, ^{127}Xe, ^{123}IMP, ^{201}Tl-DDC, ^{99m}Tc-HMPAO, ^{99m}Tc-ECD, ^{99m}Tc-MRP 20) but will also have to compete with the other imaging modalities, whose progress in this area is substantial. In reality, only if the newly announced tracer represents a quantum jump towards a better radiopharmaceutical for cerebral blood flow studies may there be a chance for the tracer to survive its initial presentation.

T691 elegantly described by Taylor et al. in this issue of the *Journal* will have to be examined within the background described above. The main advantages of T691 are rapidly apparent: the compound is labeled with ^{99m}Tc (an almost must today for CBF studies with radiotracers), the compound remains stable after reconstitution (a clear advantage over some, although not all, of the existing competitors) and sufficient compound appears to be taken up and retained by the brain for SPECT, studies for likely success in humans (bar any unexpected surprises from species specificity).

T691 does not, however, represent the needed quantum advance when compared with the known data and figures of merit for the other radiopharmaceuticals. There is no difference in the brain uptake index between T691 and ^{99m}Tc-HMPAO in rodents, and in the monkey the extraction fraction and retained fraction for T691, ^{99m}Tc-HMPAO and ^{123}IMP differ only slightly.

The experimental set-up in the paper of Taylor et al. is rather delicate. Significant differences are seen in the half-lives of retained activity in between the two experimental subjects for HMPAO and for IMP. No data are given for grey over white matter ratios for the three compounds over time, but a good quality SPECT image of a monkey brain is shown. The slice level chosen for the demonstration of the regional brain distribution of T691 is, however, rather odd. A midbrain section at the level of the basal ganglia would have been more informative.

Since the initial work with ^{123}IMP and ^{99m}Tc-HMPAO (*1-4*), much effort has gone into the conceptualiza-

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tion, design and testing of new tracers for cerebral blood flow work. What has been learned? Quite a lot of course, but it may be easier to ask what has not been learned or gained from this effort.

What is missing is a clear message that permits the development of new cerebral blood flow agents that do represent a major advance. How can one achieve brain uptake values one or two orders of magnitude greater than the ones available? How can one develop a true "microsphere" analog or true flow marker? If a clear strategy for this has not developed so far, perhaps the effort should be directed elsewhere. We need to focus on what is necessary today, but more relevant is the focus on what will be necessary in the future.

Three ^{99m}Tc-labeled cerebral flow tracers have been used in humans (HMPAO, ECD and MRP-20) (Fig. 1). The most widely used, by far, is HMPAO. It is followed by ECD, which recently was reported as efficacious in the diagnosis and localization of stroke in two multicenter trials each comprising at least 100 evaluable stroke patients (*5*).

In oncology and in the study of brain cancer, ^{201}Tl is the subject of recent focus and interest. Thallium-201 SPECT appears highly sensitive in the detection of tumour recurrence (*6*), and in comparison with Gd-DTPA enhanced MRI and ^{18}F-labeled FDG PET it proved a useful tool in the differential diagnosis between viable and recurrent tumor and radiation necrosis/inflammation (*7*). Thallium-201 brain SPECT appears further able to group patients with high-grade and low-grade gliomas (*8*). In childhood tumors of the brain, MIBI SPECT has also been advocated as a diagnostic tool (*9*), and indications exhist that it performs as well as ^{201}Tl in this context (*10*).

As already stated, there are many different image-based technologies, which can offer tomographic maps of cerebral blood flow. The consequence is clear—we are no longer alone in the effort to image cerebral blood flow. It may therefore be wise to look further and foster the design of radiopharmaceuticals which permits nuclear medicine to develop unique tests of cerebral function.

A flow-independent marker of neuronal loss will be of interest. It will need to distribute ubiquitously throughout the brain and be proportional to the total mass of viable neurones. SPECT markers of cerebral metabolism will also attract significant interest, and the recent applications of ^{201}Tl-chloride as a marker for neoplastic activity in the brain is being investigated by several groups.

Information about neuronal loss and even some aspects of cerebral metabolism may still not represent areas where the nuclear medicine methodology will be the only technology through which such data can be gathered. Unique, however, to the radioactive tracer methodology remains its ability to label and image tracer analogs of neuronal transmission. In the foreseeable future, neuroreceptor imaging will remain a unique area of research and development for nuclear medicine. No other image-based competing modality will be able to match both the unique sensitivity and specificity of the radioactive tracer method.

The development of ^{123}I-labeled neuroreceptor ligands has been quite remarkable. Expected progress would entail that ^{99m}Tc ligands will lead to more widely available neuroreceptor ligands.

Finally, nuclear medicine technology has a further important area for research and development in the brain. The monitoring of drug effect and efficacy will develop and make use of the radioactive tracer method. Treatment protocols will develop which will benefit from closer monitoring, and drug precursors will be labeled and investigated with nuclear medicine instrumentation.

With regards to cerebral blood flow studies, however, there is much to do today with existing methodologies. Figure 2 clearly points the way. Far too many studies have been performed on too small a patient sample. This must be overcome if we are to build up a meaningful body of clinical

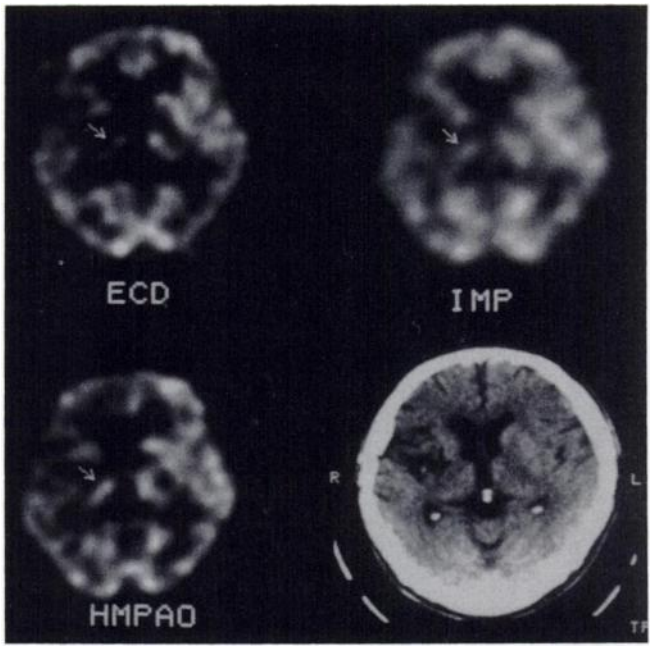

FIGURE 1. Cerebral blood flow studies obtained with ^{99m}Tc-ECD, ^{99m}Tc-HMPAO and ^{123}I-labeled IMP from the same patient. These are the most commonly used tracers in man. Note the rather similar image qualities as well as the slight deterioration with IMP. (Study supplied by Dr. H Matsuda, Kanazawa University School of Medicine, Kanazawa City, Japan.)

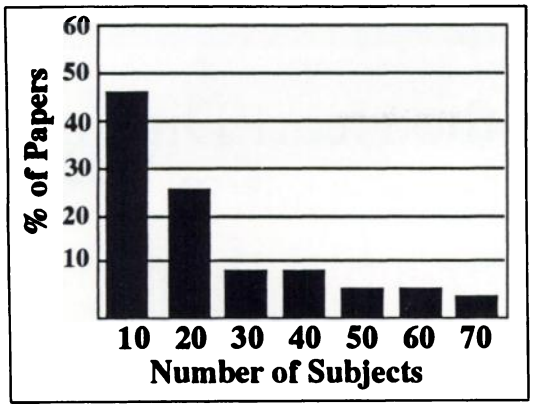

FIGURE 2. A survey of 89 published papers in 1991–1992 in the specialized literature of PET and SPECT in neurology and psychiatry. The number of subjects/patients studied in each article is plotted against the number of papers surveyed. Only a handful of manuscripts publicize data for more than 20 subjects/patients. Over 50% of all these papers discussed a sample size of less than 20!

experience. Since no single institution is currently able to cover the whole spectrum of disease, possess all the know-how, technology and infrastructure, there is only one viable solution—that of the carefully planned multicenter trial. Common protocols, common technology and common disease entities will have to be coordinated into large sample studies.

There is a need to construct a meaningful data base of normal individuals with reliable data points for each decade of age. This will have to be achieved for each gamma camera/collimator/computer/SPECT reconstruction configuration for each of the radiopharmaceuticals which will survive market forces. Notwithstanding this significant task will have to be done within the established guidelines for the administration of radioactive substances to humans, volunteer consent and general ethical and quality control considerations. This task is mandatory and urgent if we are to develop a credible base for widescale clinical application of these tracers. Figure 2 illustrates how few published studies have a statistical base involving more than a few dozen subjects. Most of these studies are soft, if not inadequate, since they do not contain homogeneous patient groups and significant age-matched controls.

A consensus should be established on the definition of a practical solution to the quantification of tracer distribution in the brain. A wide and geographically dispersed user group should be established to tackle this aim, with the involvement of two major nuclear medicine societies (SNM and EANM) in support of this project. Recent progress in the recording of simultaneous emission and transmission data sets for adequate correction for scatter and attenuation (*11–13*) will considerably help the accuracy of data collection, but it will still take two to four years before this approach will be made readily available by industry. In the meantime, a reasonable and widely used method of cortical/cerebellar ratios represents a feasible and reasonable compromise.

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