'The Secret of the NIMH'

Visit to America: The Clinical Brain Disorders Branch, National Institute of Mental Health, Washington DC

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In 'The Secret of The NIMH' (Warner Brothers) a group of laboratory mice is given a strange new compound that makes them super-intelligent and leads them to wondrous new experiences and discoveries. It was perhaps with the hope of receiving some similarly wonderful new experience that I embarked on a visit to America to seek out the secret of this place. Indeed the time spent at the NIMH (National Institute of Mental Health) Neuroscience Center was exciting and stimulating.

The story of the National Institute of Health (NIH) began in 1887 as the 'Hygienic Laboratory', a single room of the immigration quarantine facilities in New York. By 1904 this research laboratory comprised 13 staff investigating infectious diseases. From these modest beginnings the NIH was established, which is presently based in Bethesda in Washington, DC. The 70-acre Bethesda site was opened officially by President Franklin D. Roosevelt in 1940 who outlined the main aim of the NIH as to "recruit . . . knowledge and science in the service of national strength." By 1991 this goal was supported by an annual budget of over $8 billion and 16,000 personnel in 13 Institutes, covering an area of over 317 acres. The NIH has included a number of scientific celebrities, including Nobel laureates. The atmosphere at Bethesda is very exciting for a researcher from abroad, surrounded by the most up-to-date technology and some of the most talented individuals in their field.

The NIMH was established in 1949. The main part of the NIMH is located on the Bethesda site. However, the NIMH Neuroscience Center is located in the grounds of St Elizabeth's Hospital. Together with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the NIMH has made important contributions in such areas as brain imaging techniques. This has included the investigation of neurological and psychiatric disorders using new and rapidly developing imaging tools.

Clinical Brain Disorders Branch at NIMH Neuroscience Center

During my time at the NIMH, I was based with the Clinical Brain Disorders Branch (CBDB) at the NIMH Neuroscience Center in the grounds of St Elizabeth's Hospital. The latter is a large asylum for the mentally ill which was built in the early 1850s and was considered a progressive institution that readily introduced new treatments and advocated the 'humane' treatment of the mentally ill. It previously had an in-patient population of over 6,000 but this has gradually diminished. The hospital is situated in 320 acres and consists of several buildings in the Victorian style, similar to many large mental hospitals built in England at around the same time. It overlooks the Potomac River with an impressive view of Washington. The NIMH Neuroscience Center is separate from St Elizabeth's and is also known as the Neuropsychiatry Research Hospital. It houses four of the 20 branches of the NIMH, including the CBDB.

The CBDB is headed by Daniel Weinberger (Branch Chief) together with Joel Kleinman (Deputy Branch Chief), Richard Coppola (Chief of the Neuroimaging Unit), and Terry Goldberg (Chief of the Neuropsychology Unit). E. Fuller Torrey, also situated at the Neuroscience Center, has been instrumental in providing a cohort of twins discordant for schizophrenia and affective illness. The CBDB and the other branch in the Neuroscience Center are part of the Intramural Research Program of the NIMH. The NIMH also have an extramural program that provides funding in the form of grants to outside research groups.

I joined the CBDB and had the opportunity to attend their various research meetings and participated in discussions of ongoing research and potential new projects. I rapidly became involved in an MRI study which I discuss briefly below.

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Recent work at CBDB

The CBDB under the direction of Dr Weinberger has produced major work in the schizophrenia field, which is helping to elucidate the underlying neurological basis of the disorder. The brain scan activation studies from this laboratory, using the Wisconsin Card Sorting Test (WCST), have consistently demonstrated dysfunction of the frontal lobe (specifically the dorsolateral prefrontal cortex) in schizophrenia. These studies are reviewed elsewhere (Weinberger *et al*, 1991; Pantelis *et al*, 1992). Briefly, they have involved brain metabolism estimations while subjects were engaged in performing the WCST, a cognitively complex task that taps the function of this part of the prefrontal cortex. In comparison to matched controls, patients with schizophrenia were unable to perform the task and did not activate the dorsolateral prefrontal area of the brain as did normal subjects. More recently, the investigation of discordant twins has provided further evidence of DLPFC dysfunction. However, though abnormal function has been demonstrated, there has been limited evidence of anatomical pathology of this brain area (Shelton *et al*, 1988). Other investigations, including studies of the twin sample using magnetic resonance imaging (MRI) have also provided important clues as to likely subtle structural abnormalities of the temporal lobe and hippocampus in schizophrenia (Suddath *et al*, 1989, 1990). Taken together with animal studies (Goldman-Rakic, 1991), the evidence suggests that the functional deficit of the DLPFC may be a consequence of disturbance of neuronal pathways associated with prefrontal areas (Weinberger *et al*, 1991; Pantelis *et al*, 1992). Such pathways implicate subcortical structures, including medial temporal lobe structures and thalami (Weinberger, 1991; Weinberger *et al*, 1991). As well as basal ganglia and their thalamic connections with prefrontal cortex (Pantelis *et al*, 1992).

A number of recent developments at CBDB, as well as my work at the laboratory, are attempting to explore these issues further. My project involved the development of a procedure for volumetric analysis of brain MRI images. Other exciting techniques currently being developed at the NIMH have included 'functional' MRI scanning. While MRI has provided detailed resolution of organ structure, 'functional' MRI uses ultra fast MRI image acquisition techniques to provide dynamic functional scanning during physiological activation (Barrios *et al*, 1992). The development of such techniques may make redundant the functional imaging with positron emission tomography (PET) and other invasive methods.

Another procedure recently developed at the CBDB involves volume acquisition and surface rendering of thin MRI images. This technique allows reslicing of the brain in any plane and provides a method to examine the subtle differences of sulcal and gyral patterns between individuals (Bartley *et al*, 1992).

The project

Because my visit to the Clinical Brain Disorders Branch of the NIMH was time-limited, it was important to focus on one clearly defined project. Double echo brain MRI images of twins discordant for schizophrenia and also for normal twins were available. Also available was the sophisticated but cumbersome 'ANALYZE' image analysis program from the Mayo Clinic. The task was to develop a semi-automated technique allowing rapid volumetric estimations to be determined. There have been only few studies recently that have attempted to examine the volumes of individual compartments in this way (e.g. Jernigan *et al*, 1991).

The technique involved a series of steps to prepare the images for the segmentation procedure. The final images provide a four compartment separation of each brain into cortical and subcortical grey matter regions, white matter and CSF compartments. This will allow the volumes of each brain compartment to be compared for each twin and their co-twin. This procedure was presented recently at the International Congress on Schizophrenia Research (Pantelis *et al*, 1993).

Planning a visit to the US

A number of practical problems require consideration when planning such a visit. First, make certain you have an appropriate visa and that the immigration officer understands that you are not visiting as a tourist. Thus, a B2 visa is unacceptable to the NIH; a B1 or other visa is necessary, depending upon whether you are being paid by the NIH or not. A letter from the institution to be visited is almost mandatory.

Visiting America, particularly areas with which one is previously unfamiliar, is always anxiety-provoking. The hospitality I received dissipated this substantially. However, knowledge of the area can prove useful. For example, Washington has the highest murder rate in the USA and St Elizabeth's Hospital is situated in a particularly hazardous area of Washington. This posed a number of practical problems. For example, travel to the hospital without a car required careful planning. Visits out of the confines of the hospital grounds could endanger one's health and were preferably undertaken in the company of others. Despite these local customs and precautions the visit was exciting and stimulating

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and would be gladly embarked on again in the future.

Conclusion

The secret of the NIMH is not a magical tablet that endows one with super intelligence. However, being in an environment rich in research opportunities and surrounded by talented scientists does provide a great deal of stimulating thought that helps the development of one's own ideas. Good research requires good ideas, but it also requires such an enriched environment where those ideas may achieve fruition. Providing such a stimulating milieu must be seen as mandatory and not be subjected to the whims of fiscal policy. This is particularly so in the current political climate in the UK with the threatened closure of long-established centres of excellence.

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