Special Achievement in Medical Science Award

Mental illness and the sciences of brain and behavior

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In 1942, studying shock as a National Research Council fellow at Harvard with Joseph Aub, I became interested in the remarkable homeostatic reflexes that serve to preserve the flow of blood to the brain[1], an interest that was enhanced when I saw a paper by Dumke and Schmidt in which the circulation of blood to the brain was measured for the first time by means of a flow meter inserted directly into the cerebral arteries of an anesthetized rhesus monkey. When my fellowship was over I received a position in Carl Schmidt's laboratory, assisting him in further studies of perfusion and oxygen consumption in the monkey brain. Although the results were the first measurements made in a mammalian brain, I was somehow left unsatisfied.

Human cerebral circulation

Much more challenging was the *human* cerebral circulation. Although the animal heart or kidney may be adequate models of their human counterparts, the human brain is unique among that of all creatures for its capacity, its plasticity, its ability to conceptualize and create, to experience ecstasy and deep grief and to describe to outside observers the results of its inner processes. It is also the human brain that falls prey to serious disorders of these functions for which no animal models exist. But to measure the human cerebral circulation it would be necessary to develop an indirect, minimally invasive technique, applicable to normally conscious subjects.

Measurement of blood flow through the human lungs had been achieved through the Fick Principle, requiring a measure of total uptake of oxygen at the lungs and the arteriovenous oxygen difference across the lungs, which could be obtained from a catheter in the right atrium for mixed venous blood and blood samples from an artery. The arteriovenous oxygen difference across the brain could be measured, with the help of mixed cerebral venous blood from the internal jugular, but the inability to measure cerebral oxygen consumption, or even to assume its constancy in various physiological or pathological states, which were the object of study, made that approach futile.

But suppose, instead of oxygen, one used an inert and diffusible gas. The accumulation of such a gas in the brain should be independent of its metabolism and functional activity, determined instead by relatively simple physical factors such as diffusion and solubility which should be quite constant in the brain whether the subject was asleep or awake, working out a complex mathematical problem or suffering from schizophrenia. This turned out to be true, and in 1948, the first measurements of cerebral blood flow in normal human volunteers were published: A mean value for blood flow of 54 ml per 100 g per minute, or 750 ml/min for the whole brain[2]. From the blood flow and the respective arteriovenous differences, oxygen and glucose consumption could be calculated. With numerous collaborators the new technique was applied to various conditions of health and disease, including sleep, mental arithmetic, increased intracranial pressure, essential hypertension, schizophrenia, coma, and general anesthesia[3]. Although coma and anesthesia were associated with considerable reductions in cerebral oxygen consumption, in schizophrenia blood flow and oxygen consumption for the brain as a whole were not different from normal values. This brought out the most serious limitation of the new technique which treated the brain as a homogeneous organ, neglecting all of its complexity and heterogeneity. The next task became the development of a method for measuring regional blood flow.

The Fick Principle could still be used in this approach, except that venous blood from small regions would not be obtainable. Tissue concentration of a radioactive tracer, however, could be obtained by autoradiography or external counting. How closely would the unmeasured venous concentration conform to the concentration in the tissue it was draining? This question was addressed along with other issues in a review published in 1951 on the exchange of diffusible tracers between blood and tissue[4]. A mathematical expression was derived in which tissue concentration was a function of local perfusion, solubility and diffusion constants, and the past history of the arterial concentration.

An opportunity to test the equation was provided after I had moved to the National Institutes of Health and William Landau, a postdoctoral fellow, asked to work with me on regional cerebral blood flow. We recruited an unusual team of collaborators; Landau and Rowland eventually became distinguished professors of neurology and Sokoloff's contributions to regional cerebral metabolism are world famous. Trifluoriodomethane labeled with ^{131}I was used and a quantitative autoradiographic technique was developed and values were obtained for perfusion in 28 structures of the cat brain[5]. During photic stimulation done by Sokoloff, substantial increases in the perfusion of the whole visual system were seen in what was the first 'imaging' of cerebral functional activity[6] (Fig. 1).

Raichle and colleagues were the first to apply this technique,

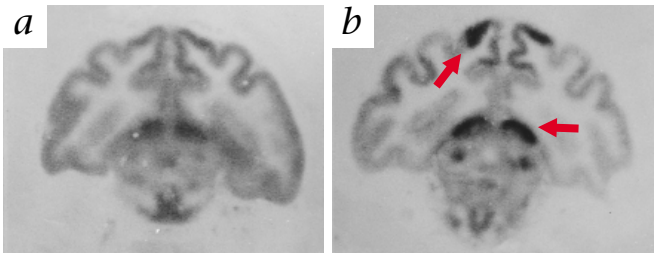


Fig. 1 Autoradiogram of brain of a cat (***a***) resting and (***b***) during photic stimulation. Radiographic density is correlated with perfusion[5]. There are high rates in the superior colliculi and visual cortex, indicating highly increased functional activity in the visual system (arrows). From Sokoloff[6].

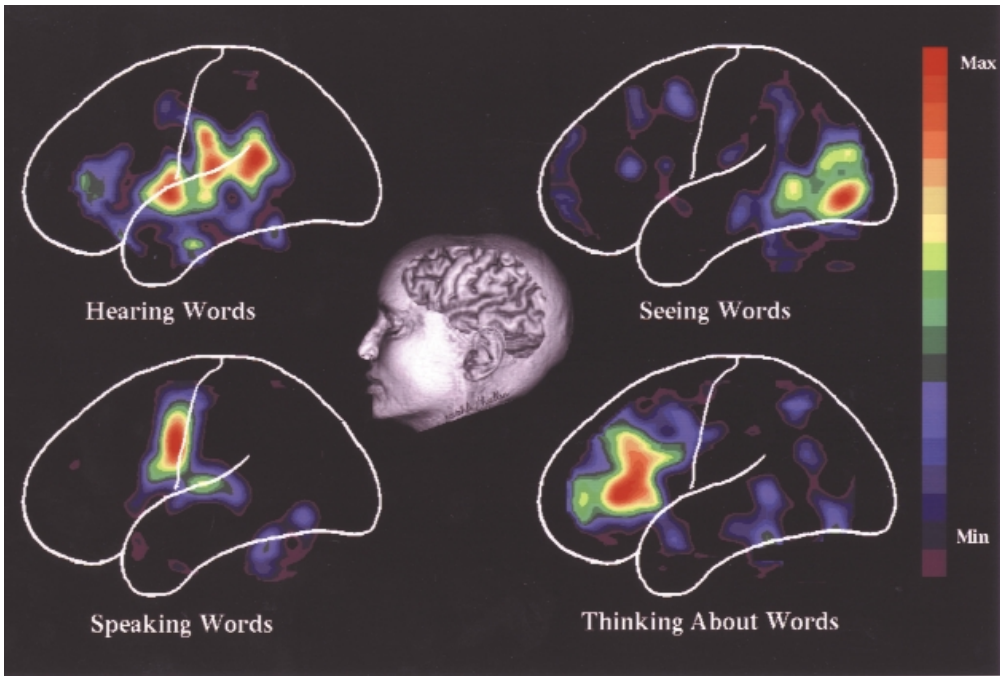


Fig. 2 Regional blood flow in the human brain defined by PET scans using the autoradiographic technique with ^{15}O water as a tracer[7]. Increases in blood flow occur in the auditory and visual cortex during respective sensory stimulations. Speaking is accompanied by increased perfusion in the motor area, and thinking about words affects the frontal area.

which they called "the autoradiographic technique," to the normal human brain, using ^{15}O-labeled water to demarcate regions of activation during sensory input and cognitive tasks[7] (Fig. 2). Sokoloff went on from cerebral perfusion to develop the deoxyglucose technique to measure and visualize local metabolic activity. Both of these approaches were successful in demonstrating functional activity in the human brain. Thus it became possible to measure circulation and metabolism and to visualize functional activity throughout the uniquely human brain, some 20 years after I dreamed about it, with obvious implications for physiology, functional anatomy, cognitive psychology and neuropsychiatry.

Establishment of the intramural research program at the NIMH

In 1950, my research was interrupted by a visitor from Bethesda. The studies of cerebral blood flow in schizophrenia had come to the attention of the National Institutes of Health, and Robert Felix, the director of the newly founded National Institute of Mental Health, came to invite me to join his Institute as its first scientific director. I had been perfectly happy with Julius Comroe at the University of Pennsylvania but felt that I couldn't decline the offer without a visit to Bethesda. There I conferred with James Shannon and Harry Eagle, scientific directors of the Heart and Cancer Institutes, visited the 200 laboratories under construction for the Mental Health Institute and came away feeling very fortunate to be given the unprecedented opportunity of planning and directing as I saw fit what Felix called "the greatest institution for the study of the brain and behavior that the world has ever seen." There was little doubt that it would be the largest, but whether it would be the greatest remained to be seen.

Research on mental illness was an open field. Clinical research was largely descriptive and biological psychiatry could be characterized as the premature application of inadequate biological knowledge to problems not yet shown to be medical in origin. The new institute would need scientific clinical research, but for that to be meaningful there was the greater need for considerably more fundamental knowledge in the sciences of brain and behavior. I could think of no better investment of the new and unprecedented resources placed at my disposal than to establish a broad program of basic research representing all of the disciplines on which psychiatry depends.

My appointment and the direction it denoted elicited mixed reactions. Psychiatrists were curious or concerned. I received one note from a highly regarded analyst urging me "not to drive another nail into the coffin of psychiatry." There were plaudits, however, from fields outside of psychiatry and many younger scientists saw opportunities for their research in the new institute and applied for appointments, happy to learn that they would have complete academic and scientific freedom in this government institution. Some twenty-five of those appointed were eventually elected to the National Academy of Sciences, four won Lasker Awards, and two won Nobel prizes. That program has sometimes been credited with playing a major part in converting American psychiatry into the medical science it is today.

Genetic factors in the etiology of schizophrenia

The well-known observation that the major psychoses, schizophrenia and manic-depressive illness tend to show a familial distribution led early investigators to assume the importance of hereditary factors in their etiology. The increased emphasis on life experience and psychosocial influences that then occupied psychiatric thinking left little room for heredity, and saw in the clustering in families clear evidence for the transmission of these disorders from parents to children within the rearing process.

A small school of thought remained unpersuaded, however, pointing to the substantial number of well siblings reared by the same schizophrenogenic parents. There were also several studies of the concordance of schizophrenia between monozygotic and dizygotic twins with the former showing about 50% concordance and the latter, fraternal twins, carrying 10% concordance. The 50% discordance was seized upon, however, as representing definitive evidence for the operation of environmental factors, whereas the high concordance in identical twins could represent the pervasive sharing of the environment that identical twins experience. They look alike, their parents treat them alike and dress them alike. They are usually in the same class and have the same friends. It is difficult to

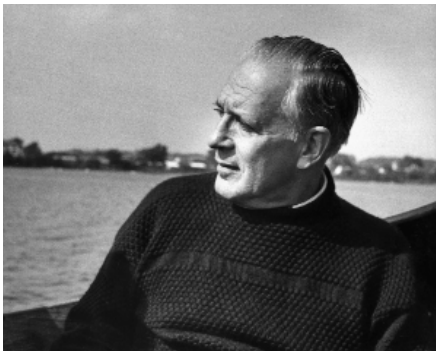
tell how much of their high concordance for schizophrenia was the result of the genes or the environment they shared.

I tried to think of a way to separate genetic from environmental factors in family studies and suddenly realized that adoption does just that. An adoptee shares his genetic endowment with his biological family but his environment with another family. If schizophrenia runs in families because of shared genes, it should be found in the biological family of the schizophrenic adoptee. If caused by rearing or other components of the family environment, it should be found in the adoptive family. It seemed reasonable that with appropriate controls to remove ascertainment, selective and subjective bias, adoption could indeed disentangle genetic from environmental influences in the family. I proposed such a study with all the necessary controls and pointing out one further but crucial stipulation: "Perhaps only a study on a national scale would provide the requisite number of cases."[8]

Two other scientists at NIMH, David Rosenthal and Paul Wender, interested in the nature–nurture question in schizophrenia, willingly joined me in adoption studies with different foci. It did not take long to realize that it would be difficult if not impossible to undertake such studies in America. We heard about the wonderful demographic records maintained in Denmark. I flew to Copenhagen in 1962, meeting with Fini Schulsinger, chief of psychiatry at the Kommunehospitalet there, who showed me samples of the records, agreed to work with us on the project and secured our access to the records with guarantees of confidentiality.

My colleagues and I have been engaged in several controlled studies, in Copenhagen and in the rest of Denmark, that examined the incidence of schizophrenia in the biological and adoptive relatives of schizophrenic adoptees[9–11], and each has found that schizophrenia is concentrated in their biological families rather than in their adoptive relatives. We also find a highly significant increase in the prevalence of both chronic and latent schizophrenia in those who were related genetically to adoptees who had developed classical chronic schizophrenia.

These diagnoses were made, by investigators 'blinded' to subject identity, from extensive psychiatric interviews and were based on the descriptions of Kraepelin for dementia precox or Bleuler who called it schizophrenia, and for the milder



Seymour Kety in Fini Schulsinger's boat near Copenhagen, 1962.

syndrome with some of the features of schizophrenia that Bleuler called latent schizophrenia. The more recent term 'schizotypal personality disorder' is comparable to our diagnosis of latent schizophrenia from which it was largely derived. A finding of considerable importance is the apparent genetic specificity shown by the classical syndrome of schizophrenia as it was originally described by Kraepelin and Bleuler, which was found almost exclusively in the biological relatives of such adoptees[12] (Table 1).

Table 1 Diagnoses in the relatives of chronic schizophrenic index probands and controls in the national sample of adoptees

Relatives	Schizoid personality	Latent schizophrenia	Chronic schizophrenia	Total relatives
Biological, of 46 chronic schizophrenic adoptees	12 4.4%	27 9.8% 0.00003*	14 5.1% 0.0008*	275
Biological, of 49 control adoptees	13 5.1%	4 1.6%	1 0.4%	253
Adoptive, of 46 chronic schizophrenic adoptees	0	2 1.8%	0	111
Adoptive, of 49 control adoptees	0	2 1.6%	0	124

*Fisher exact 1-tailed *P* for biological index and control relatives.
Reprinted from the Journal of Psychiatric Research[12].

Environmental influences

Evidence that genetic factors are important in etiology does not argue against the existence of significant or essential environmental influences. Many of these have been suggested, some are supported by empirical evidence, although no single environmental factor has been shown to play an essential part in a substantial segment of the disorder.

Birth injury[13], viral infection during gestation[14], dietary factors, auto-immune processes[15,16] and developmental mishaps[17] have been the basis of plausible etiological hypotheses supported by provocative and often compelling evidence. The high prevalence of schizophrenia in the lower socio-economic classes of large cities[18] has suggested an etiological role for some of the environmental stresses that exist to a greater extent in these classes. The apparent effect of these factors on the etiology of schizophrenia, however, would be exaggerated because several infectious diseases, especially those of viral origin, occur significantly more frequently in lower socio-economic classes.

Although parental characteristics and rearing have been widely blamed for the development of schizophrenia, no well-controlled evidence substantiates the premises and children born of a schizophrenic mother but reared by foster parents or institutions free of mental illness have no diminished incidence of schizophrenia[19]. Conversely, children with and without risk for schizophrenia reared by psychotic mothers have no elevated incidence of schizophrenia[20].

Thus, schizophrenia continues to pose many unanswered questions. Although the evidence is good for the operation of both ge-

netic and environmental factors, no genetic locus has been identified, and the mode of genetic transmission remains enigmatic.

In sharp contrast to the absence of cerebral structural or functional abnormalities only twenty years ago, there are reasonably well-defined morphological, metabolic and physiological changes, demonstrable by new and older techniques, and though no one among them is pathognomic, each opens the way to further investigation and knowledge. Neuropsychological functions, made definable by quantitative techniques, are showing some of the characteristics of 'genetic markers'[21]. Smooth pursuit eye tracking[22,23] and continuous performance[24] are among the challenges which show a familial disturbance. At the clinical level, much of the confounding accretions to classical schizophrenia which developed over the objections of Kraepelin and Bleuler are being stripped away, permitting the classical syndrome to emerge, if not suffused with new light, at least with many of the former shadows better illuminated.

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