Prospects for Neurology and Psychiatry

W. Maxwell Cowan, MD
Eric R. Kandel, MD

It is not generally appreciated, even among physicians, that in terms of morbidity—to say nothing of personal suffering—disorders affecting the nervous system are among the most serious of all health problems in developed societies. While stroke ranks third behind heart disease and cancer among the leading causes of death, disorders of the nervous system, when taken as a whole, account for more hospitalizations, more long-term care, and more chronic suffering than nearly all other disorders combined.

It is difficult to obtain precise figures for the incidence of many of the disorders that affect the nervous system, but the following estimates, derived from a recent report prepared by the Dana Alliance for Brain Initiatives and from written testimony presented, in April 2000 to the House Appropriations Subcommittee on Labor, Health and Human Services by Dennis W. Choi, Head of Neurology at Washington University School of Medicine and currently president of the Society for Neuroscience, indicate the magnitude of the problem posed by such disorders and their estimated economic burden on the US economy.

Every day about 1200 Americans become victims of stroke. Of the almost half a million individuals who annually suffer strokes, about one third die and one third are permanently disabled. The annual cost amounts to $30 billion per year (to judge this only in the basest of terms—lost earnings and the cost of health care).

Alzheimer disease, which is now the fourth leading cause of death among adults, affects over 4 million Americans at an estimated annual cost of over $90 billion; by the middle of the 21st century it is likely to affect as many as 14 million people unless effective measures for its treatment or prevention are discovered.

Serious depression (including manic depressive illness) affects 17 million Americans at an estimated cost of $44 billion for treatment, disability, and loss of productivity; importantly, as many as 1 in 5 individuals suffering from manic depressive illness will die by suicide. An estimated 15 million people suffer from drug dependence (including alcoholism) at an annual cost of over $240 billion. Care for children suffering from fetal alcohol syndrome—a direct consequence of maternal alcoholism, by itself costs $2 billion. According to the National Institute on Drug Abuse, 1.5 million Americans are chronic users of cocaine.

Just under 10% of the population suffers from deafness or some other hearing disability, and just over 3% experience blindness or other serious visual impairment. About 4% of all malignant cancers affect the brain, and of those with primary brain tumors, 12000 die each year. Severe pain costs the
country about $65 billion annually, including the loss of at least 4 billion workdays, over 500 million by full-time employees. Epilepsy affects 2.5 million Americans at an annual cost of $3 billion. Multiple sclerosis, which commonly affects individuals in their 20s and 30s, currently involves 350,000 Americans at an estimated cost of $5 billion. Traumatic injury to the brain and spinal cord, mostly due to automobile or motorcycle crashes and gunshot wounds, affects as many as 1.2 million people each year; a high proportion of those injured, including many teenagers and young adults, are left permanently impaired at an annual cost of $35 billion. Parkinson disease affects a half a million individuals at a cost of $5.6 billion. Schizophrenia that usually manifests itself in the late teens or early adult life affects more than 2 million people in the United States; it also accounts for a considerable number of homeless individuals and a significant number of suicides each year. Schizophrenia costs an estimated $30 billion per year.

An estimated 9 million children and adolescents are affected by developmental or behavioral disorders, including cerebral palsy, autism, and various forms of mental retardation whether genetic (such as Down syndrome and fragile X syndrome) or due to some intrauterine or perinatal insult to the brain. It is estimated that only one third of these individuals are receiving appropriate medical care.

To this extensive list we might add a large number of less common disorders such as Huntington disease (HD), Tourette syndrome, amyotrophic lateral sclerosis (Lou Gehrig disease), Creutzfeldt-Jakob disease (the human counterpart of mad cow disease), the spinocerebellar ataxias, and a host of other disorders.

Simply listing these various disorders and their economic impact tells nothing about the suffering—usually long lasting or recurring—experienced by the patients and by the families who take care of them. And as the population as a whole ages, the burden imposed on society by neurological and psychiatric illness is bound to place a severe, if not crippling, strain on the entire health care system and the associated social services. Fortunately many recent advances in the biomedical sciences, and in the field of neuroscience in particular, hold promise of relieving what would otherwise be a very gloomy prospect. It is with these developments, and the future developments that will build upon them, that this brief review of the prospects for neurology and psychiatry in the first 2 decades of the 21st century is concerned.

Given the limitations of space we can at best deal only very broadly with what we think the most promising avenues for further progress are likely to be. At the same time we recognize that at any time some unanticipated new insight or some imaginative technical innovation may dramatically alter both the clinical and research landscape. And while many of the advances will undoubtedly come from research directed at the nervous system itself, important advances are just as likely to come from other areas of biomedical research.

Improvements in the prevention and treatment of stroke are worth citing in this context. Since strokes generally occur against a background of cerebrovascular atherosclerosis, the most immediately effective benefit has come from studies of the underlying causes—genetic, metabolic, and nutritional—of atherosclerosis in general and from the recognition of the importance of hypertension as a major contributing factor. The principal advance in the treatment of strokes in the recent past has been the early administration of the tissue-type plasminogen activator enzyme (tPA) (activase)—an approach that followed rather directly from the use of the enzyme in the treatment of myocardial infarcts. On the other hand, the use of inhibitors of glutamate receptors to limit the excitotoxic action of this excitatory neurotransmitter on neurons beyond the immediate area of infarction has so far proved to be rather disappointing. This is not to imply that new drugs of this kind may not yet prove to be effective. The history of science and medicine has taught us that the disappointments of today are often the prelude to tomorrow’s success.

The Promise of Neuroscience for Neurology

Whereas stroke and a number of other neurological conditions (such as the nervous system complications of diabetes mellitus) are most likely to benefit from further developments in internal medicine and in the underlying basic science of molecular cell biology, most neurological and psychiatric disorders will depend largely upon advances in neuroscience for their elucidation, prevention, and treatment. Before considering some of the contributions that we anticipate neuroscience will make to neurology and psychiatry, it may be instructive to comment on the recent history of neuroscience itself: how the field emerged in the period following World War II, and how it has already influenced its cognate clinical disciplines.

As we have pointed out elsewhere, the roots of modern neuroscience reach back to the latter part of the 19th and the early years of the 20th centuries when the concept of the neuron as the cellular basis of all nervous systems was established and the essential features of nerve cell signaling and synaptic transmission were laid down, together with the emerging insight of the fundamental role played by neuron-neuron interactions in the integrative action of the nervous system. But beginning in the 1950s the hitherto largely independent disciplines of neuroanatomy, neurophysiology, neurochemistry, pharmacology, and experimental psychology that for so long had been separated by methodological and conceptual differences, began to come together. This movement originated first at the Walter Reed Army Institute of Research when an extraordinary group of scientists drawn from these various disciplines were brought together by David
McKenzie Rioch in an attempt to bring to bear on the study of stress and mental diseases, all the available approaches in brain science. This was followed in the early 1960s by the creation, at the Harvard Medical School, of the first department of neurobiology which, under the inspired leadership of Steven Kuffler, succeeded in transcending the traditional disciplinary boundaries. The emerging multidisciplinary field was named neuroscience by Francis O. Schmitt,4-7 who conceived of the Neuroscience Research Program that he had created, as the harbinger of a new scientific discipline.

Three measures of the success of the new field are (1) the astonishing growth of the Society for Neuroscience, which began in 1968 with about 600 members and by the end of the century had more than 25000 members; (2) the appearance of literally dozens of new scientific journals; and (3) the formation of new departments or programs of neuroscience at almost every university or medical school in the United States.

From the beginning, the field had as one of its primary goals the elucidation of the biological basis of behavior and a natural outcome of this was the emergence within the field (or, as some would say, the convergence into the field) of the subdiscipline now commonly referred to as cognitive neuroscience. Cognitive neuroscience has as its principal concern the biological foundations of such “higher brain functions” as perception, the organization of motor performance, affect, language, learning and memory, and how these cognitive functions are impaired in various brain disorders. In the United States these developments were fueled by generous public support through the National Institute for Neurological Disorders and Stroke; the National Institute for Mental Health (both of which were founded in 1950); and by other institutes concerned primarily with vision, hearing, and various forms of addiction, as well as support from a number of private agencies, such as the McKnight Foundation, the Klingenstein Foundation, The Pew Charitable Trust, the McDonnell Foundation, and most recently, the DANA Foundation.

The past 4 decades have witnessed considerable progress, especially in our understanding of the basic mechanisms involved in the differentiation and growth of neurons, in the ways in which they form the precisely organized patterns of connections that characterize the mature nervous system, and especially in the molecular mechanisms underlying neuronal signaling and synaptic transmission. The study of the various systems that comprise the brain and spinal cord has, understandably, been more difficult, but considerable progress has been made in elucidating the functional organization of the major sensory systems (especially the visual system) and to a lesser extent the many systems involved in the control of bodily movements, and those implicated in affective behavior.

Most of this progress is directly attributable to various technological advances including improved methods for tracing connections between different parts of the brain, for visualizing individual neurons in living brain preparations, for recording the activities of neurons—especially for recording activity in the brains of conscious behaving animals, refined methods for studying the behavior of single ion channels and the receptors for certain neurotransmitters, and new methods for simultaneously recording the activity of large numbers of neurons. In the case of the intact human brain, the development of noninvasive methods, such as positron emission tomography (PET scanning) and functional magnetic resonance imaging (fMRI) has enabled investigators for the first time to identify regions of the brain that are active during the performance of various cognitive, affective, and other tasks.

By general consent, however, the most significant impact in the past 2 decades has come from the application to the nervous system of the techniques of molecular genetics and molecular cell biology. These have permitted the identification, cloning, and sequencing of an ever-increasing number of neural genes, the creation of transgenic animals, the knocking out of selected genes by homologous recombination, and of conditional mutations directed at specific parts of the nervous system. Collectively the methods of molecular genetics have provided more new information and a deeper understanding of almost all facets of neural structure and function than at any period in the past half century or more (see Albright and colleagues8 for a recent summary of these and related developments in neuroscience).

Of particular importance has been the use of these molecular methods to identify many of the genetic loci and, in some cases, specific mutations responsible for known neurological disorders, such as HD, familial forms of Parkinson disease, the spinocerebellar ataxias, various muscular dystrophies, and Alzheimer disease. And we make bold to say that, in our judgment, it is these and related developments in molecular biology that are likely to account for most new advances in both neurology and psychiatry in the next quarter century.

Given that by most estimates more than half of the 40000 to 50000 genes in the human genome are expressed either exclusively or preferentially in the brain, we may confidently anticipate that when the entire sequence of the human genome becomes available and has been appropriately annotated—(now anticipated to occur within the next 2 or 3 years) progress, not only in neuroscience, but in neurology and psychiatry, will proceed at an unprecedented pace.9 So rich will this harvest be, that it is not too rash to state that it will completely transform both clinical disciplines and put them on the sound scientific foundation that has long been one of their principal, if often unstated, goals.

Concurrently, the identification of the protein products of these genes will provide new targets for drug development. The identification of the gene involved in a disorder is an essential first step toward its elucidation; but it is only the first step, and in many cases it has
proved to be the easiest step. Discovering the product of the gene, when and where it is expressed, how its production is regulated, and what it actually does are usually much more difficult. Further progress toward these ends will likely depend heavily on developments in the newly emerging fields of functional genomics and proteomics.

Although it was not the first neurologically important gene to be identified, the discovery of the gene for HD and the subsequent identification of the encoded protein, huntingtin, is one of the most striking examples of the great potential of human neurogenetics. As is well-known, HD is an autosomal dominant disease marked by progressive motor and cognitive impairment. Death commonly occurs about 15 to 20 years following the onset of symptoms. The disease commonly first manifests itself in middle age, after the reproductive years, leaving an intolerable burden of uncertainty on the children of a parent with HD. The motor symptoms (and possibly the cognitive dysfunction) are the result of massive cell death in the caudate nucleus and putamen.

In the 1980s Nancy Wexler and her colleagues undertook an extensive study of a large, extended family of individuals suffering from HD on an island in northwestern Venezuela. Blood samples from many of these individuals enabled Wexler’s collaborators to identify and localize the HD gene to near the end of the short arm of chromosome 4, using the method of restricted fragment-length polymorphisms (see Gusella et al). Establishing the genetic locus of HD made it possible to identify individuals carrying the disorder long before it manifested itself clinically. However, it took almost a decade before the actual gene was isolated and shown to encode a protein of 350,000 kd, that is expressed not only in the brain but also in many other tissues. Of particular interest was the finding that the first exon of the gene contained large numbers of repeats of the trinucleotide sequence CAG encoding the amino acid glutamine. In normal individuals there are fewer than 40 such repeats, but in patients with HD the number may range from 40 to 80 or more. (Individuals with more than 60 CAG repeats usually develop HD as juveniles.) Family studies made it clear that the number of such repeats increases from generation to generation, which provided a sound genetic basis for the clinically recognized phenomenon of anticipation, in which a disorder occurs progressively earlier, and often with greater severity, in succeeding generations.

Trinucleotide CAG repeats of this kind were quickly discovered in a large number of other neurological disorders including spinal and muscular atrophy, the spinocerebellar ataxias 1, 4, 6, and 7, and dentatorubro ataxia. Other trinucleotide repeat disorders such as fragile X mental retardation and myotonic dystrophy involve different trinucleotide sequences, but in every instance it seems that the excessive number of repeats causes an instability in the gene that affects its expression. In the case of CAG repeats there is evidence for a progressive accumulation of glutamine tracts within the neurons that may ultimately lead to their death (see Zoghbi and Orr).

We have discussed HD at some length, not only because of the dramatic history of its discovery but also because it illustrates how the identification of the genetic basis of a disorder can often lead quite rapidly to the analysis of the resulting pathogenesis. This has been aided by the creation of animal models in the case of HD in transgenic mice and, interestingly, also in fruit flies. Studies have provided a clear paradigm for the future study of many other neurological disorders where the function of the altered gene product is not known. In other cases where the genetic analysis builds on a long history of physiological and biochemical studies (as in the case of the recently recognized class of disorders known as channelopathies, and in certain neurological disorders such as Leber hereditary optic neuropathy and myoclonus epilepsy, which are due to mutations in mitochondrial genes), progress can be much more rapid and the underlying pathophysiology more clearly defined.

The Promise of Neuroscience for Psychiatry

Because of the remarkable success of molecular genetic approaches in neurology, there has been considerable enthusiasm for also applying these approaches to psychiatric disorders. However, at the moment, genetic approaches have been successful primarily for monogenic disorders such as HD and the channelopathies. Psychiatric diseases such as schizophrenia, manic depressive illness, and borderline personality are clearly polygenic disorders, and the identification of the relevant combination of genes involved in these disorders has proven to be much more difficult than in monogenic disorders. This intrinsic difficulty has not been helped by the several early claims of the finding of a genetic locus that have, on reexamination, not been substantiated. Fortunately, while the search for the relevant genes continues to be vigorously pursued in many centers, the availability of sequence data for the human genome and the development of whole genome scanning methods make it reasonable to predict that within the next 20 years we should, for the first time, be able to provide a mechanistic basis even for the polygenic disorders.

Indeed, now, after many years of slow and disappointing work, we are already beginning to see early signs of progress. This has come from 2 directions: (1) studies of chromosomal abnormalities and (2) studies of the pedigrees of families greatly enriched for schizophrenia.

The Search for Chromosomal Abnormality

A classic method used for identifying disordered genes in leukemias and other forms of human cancer (see for example Rowley) has recently received renewed interest in schizophrenia with the search for chromosomal abnormalities due to translocations and deletions. This interest began in 1988 with the report by Anne
Bassett and her colleagues15 of an Asian family in which 2 members who had schizophrenia also had a partial trisomy of chromosome segment 5q11.2 to 13.3 caused by an unbalanced translocation of the long arm of chromosome 5.

In 1994, Maria Karayiorgou and her colleagues16,17 extended this approach with the finding of 2 small deletions at chromosome 22q11 in a sample of 100 unrelated schizophrenic patients. The frequency of these microdeletions in the general population is thought to be rare, about 2 in 10000, and, in fact, no deletions were found in her sample of 200 healthy controls. Bassett and Chow18 recently summarized a number of subsequent studies of this region, which indicate that individuals with 22q11 microdeletions have twice the risk of developing schizophrenia compared with a first-degree relative of patients with schizophrenia. Among patients with schizophrenia, the 22q11 microdeletions appear to be enriched about 80 fold. Thus, deletions in this region appear to represent an underrecognized cause of schizophrenia, and some combination of genes within this region is likely to be causally involved in the susceptibility to schizophrenia.19

What, then, are the genes of this region? The critical locus on chromosome 22q11 is about 1.5 Mb in size and contains about 50 to 80 genes. What is of particular interest is that the psychiatric phenotypes associated with deletions in this locus are not limited to schizophrenia. The region also contains genes that predispose for obsessive-compulsive disorder (OCD).20 Two genes in this region are noteworthy: the genes for catechol-O-methyltransferase (COMT) and for monoamine oxidase (MAO). Both of the proteins encoded by these genes are involved in the metabolism of biogenic amines, and, surprisingly, both genes reveal a sexually dimorphic pattern of susceptibility. This suggests that gender differences may be extremely important in determining genetic predispositions, perhaps not only in OCD but also in other psychiatric disorders. An allele of the COMT gene that results in a 3- to 4-fold reduction in enzyme activity is associated with susceptibility to OCD, particularly in men.20,21 By contrast, an allele of MAO that is linked to high enzymatic activity also predisposes to OCD in men. Consistent with the well-established action of MAO inhibitors as antidepressants, this association was found to be particularly marked in men with OCD who also suffered from a major depressive disorder.21

The Search for Pedigrees Enriched in Specific Mental Illnesses. Recently Linda Brzustowicz and her colleagues22 discovered a major locus on chromosome 1 for susceptibility to schizophrenia with a maximal heterogeneity logarithm of the likelihood of linkage (log) score of 6.50. This linkage is very powerful, 100 times stronger than any reported in earlier studies, and may be sufficient to allow for positional cloning of the underlying susceptibility gene. This locus was discovered by studying a set of 22 Canadian families that were of Celtic and German origin and who had many relatives diagnosed with some form of schizophrenia. This study demonstrates the importance of careful family selection. Because the effort to identify pedigrees with several affected individuals in several generations requires a great deal of effort, most genetic studies of schizophrenia have, in the past, focused instead on gathering large numbers of small nuclear families with pairs of affected siblings. But large numbers of small families only seem to increase the chance of having a sample that is heterogeneous, both clinically and genetically. With many small families, a significant portion of the sample is not linked to a particular locus, so that the power to detect linkage is greatly reduced.

Even though these results represent a promising new direction along the tortured road in search for susceptibility genes in schizophrenia, it is important to emphasize that even the identification of 1 or 2 genes (welcome as this is) may not be sufficient to delineate fully the pathophysiological mechanisms underlying schizophrenia. Experience with familial parkinsonism and familial amyotrophic lateral sclerosis is informative in this context. The initial hope was that when the causative genetic mutations in these familial disorders were discovered, this would provide fairly immediate access to an understanding of the far more prevalent sporadic forms of Parkinson disease and amyotrophic lateral sclerosis. Unfortunately, this has not proved to be so, and the identification of the underlying pathogenesis in the sporadic cases may turn out to be extremely difficult, involving not only yet-to-be identified genes but also a variety of as-yet-unknown environmental factors.

Nevertheless, we can anticipate that the extension of the Human Genome Project to the analysis of polymorphisms in large numbers of interesting genes will throw light on this issue and also on the differences in the response of patients to particular therapeutic interventions, such as the use of lithium in manic depressive illness and of various antidepressive agents in this and other forms of severe depression.

Toward a Molecular Neuropathology for Schizophrenia. Studies over the last several decades have revealed several interesting neuropathological abnormalities in schizophrenics (see Cowan et al3 and Lewis23). The most consistent of these is an enlargement of about 20% to 40% of the lateral and third ventricles, with a median increase in the lateral ventricles of about 40%.24,25 Paralleling the ventricular enlargement, there is a reduction in total brain volume of up to 5% that is most evident in the cerebral cortex. The largest reduction appears to be in the medial temporal lobe including the hippocampus, the amygdala, and the parahippocampal gyrus as well as in the superior temporal gyrus and the prefrontal cortex.26 These abnormalities have been observed early in the patients’ illness, often as early as their first psychotic episodes and prior to the first use of medication, indicating that these abnormalities are not the secondary
consequences of either chronic psychiatric illness or pharmacological intervention. Indeed, ventricular enlargement tends to be evident even in nonpsychotic individuals at high risk for developing schizophrenia.

Needless to say, ventricular enlargement alone is not diagnostic of schizophrenia; even though the mean values differ between schizophrenic individuals and normal subjects, there is a significant overlap in the distribution of values for ventricular size in the 2 populations. Only when the comparison is ideal, as in the case of identical twins who are discordant for schizophrenia, does the difference between the individual with the disease pop out as a clear increase in ventricular volume compared with the nonpsychotic twin. In addition, it should be pointed out that increased ventricular volume is not limited to schizophrenia, but is found in a number of other brain disorders.

In the search for more specific neuropathological changes associated with schizophrenia, investigators have recently focused their attention on the prefrontal cortex, which is one of the areas of gray matter reduced in volume. Among other things, this association is thought to be important for working memory, a form of attentional memory that is impaired in schizophrenia and even in the nonpsychotic offspring of parents with schizophrenia. Working memory is reflected in the ability to maintain information transiently in consciousness so as to guide a subsequent response.

Consistent with an impairment in working memory, MRI studies have revealed that the volume of the prefrontal cortex is decreased in the majority of patients with schizophrenia. These studies, and postmortem anatomical studies, make it clear that the decrease in volume is not due to a reduction in cell number but to a decrease in synaptic connectivity in the prefrontal cortex. Since the major input to the prefrontal cortex comes from the medial thalamus, part of the underlying neuropathology is now thought to originate in the thalamus. This is supported by the postmortem findings in the brains of schizophrenics of decreased levels in the prefrontal cortex of synaptophysin, a marker protein for presynaptic terminals. Recent postmortem studies suggest that, in fact, there is a parallel reduction in both the volume and the number of cells in the mediodorsal nucleus of the thalamus, the principal source of thalamic input to the prefrontal cortex.

Imaging studies of the prefrontal cortex have shown also that emotion and cognition activate separate areas of the medial frontal lobe. In some studies, the cognitive and emotional areas in this region appear to be mutually inhibitory; thus, cognitive tasks tend to reduce blood flow in the areas related to emotion and vice versa. PET scans of patients who have never been on medication and who are still in the early phases of schizophrenia have also shown a defect in the left globus pallidus, an area that is associated with the outflow of the major dopaminergic circuit modulating cellular activity in the medial frontal lobe. Abnormal function in this component of the dopaminergic outflow might contribute to the neglect of the right side of space, which is frequently seen in early schizophrenia and perhaps also to the changes in circuitry within the prefrontal cortex found in the brains of schizophrenic patients.

Clinical Neuroscience and the Unification of Psychiatry and Neurology

We mentioned earlier that at any time soon some new discovery could radically alter our perspectives of neurology and psychiatry, so it may be fitting to conclude this article with an example of 1 such development. This is the discovery that in certain regions of adult human brain there are persistent neural stem cells that can give rise to various classes of neurons and glial cells. Although there had long been evidence for the continued proliferation of neurons in rodent brains (and also evidence that the newly formed neurons can form the appropriate connections), the finding of stem cells in the human brain has given a whole new impetus to the potential use of such cells for the repair of damaged brain tissue. The transplantation of fetally derived dopaminergic neurons to treat Parkinsonism has already proved to be successful in some patients, so the prospect of using natural or genetically manipulated stem cells in the treatment of other neurological disorders holds considerable promise for the future. This is an especially promising approach to the problem of neural repair if used in conjunction with 1 or more of the known neuronal growth factors such as nerve growth factor, the brain-derived neurotrophic factor, and the glial-derived trophic factor.

That so many of the advances in neuroscience and genetics have suggested new diagnostic and therapeutic approaches that were unimaginable just a decade ago is grounds for our optimism that the ensuing decades are likely to be remembered as the time when, at long last, neurology and psychiatry came into their own, as among the major beneficiaries of the revolution in biological science that began in the early 1950s and continued at an ever-accelerating pace through and beyond the turn of the 20th century.

As has been the case of neurology, we believe that a framework based on neuroscience will prove to be important for psychiatry as well. To function effectively, psychiatrists of the future will need more than just a nodding familiarity with genetics, imaging, and neuroscience. The knowledge they will need may be different from that of a well-trained neurologist, but fully comparable in the level of expertise. In fact, it is likely that in the decades ahead we will see a new degree of cooperation between neurology and psychiatry. This cooperation is likely to have its greatest impact on patients for whom the 2 approaches, neurological and psychiatric overlap, such as in the treatment of autism, mental retardation, and the cognitive disorders associated with Alzheimer and Parkinson diseases. We...
therefore believe that with further growth, neuroscience will most likely serve to bring neurology and psychiatry even closer together.

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