Psychiatry's Remarkable Journey: The Past 40 Years

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It is remarkable when one day you reflect and find that you have been working in a field for more than 40 years. You can read history books, trace a field's development, and study change. You try to visualize what it was like in the earlier days and how things evolved and how events relate to each other. But the perspective you gain when you have lived through an era or several eras—and therefore have the history in your head—is rather startling. You are in a sense your own history book.

As I was reading last summer, I was impressed by books such as *The Guns of August*, written by Barbara Tuchman, in which the author was able to relate the events of the beginnings of World War I backwards and therefore to relate a tumultuous era to these earlier events. The book seemed in turn to forecast the future—the reemergence of militarism in Germany in the 1930s and the trajectory that led to World War II. Thus Tuchman's outstanding book has a long sweep. Thinking back on it, we have all seen quite a sweep in psychiatry in recent decades.

So, in talking about our field, it is instructive to reflect on what this field was like in the period 1955 to 1960 and what it is like today. Perhaps taking that look, plus looking at the various factors that impinge on our field, can help us understand where the field is going and how those of us who want to have some constructive influence on it can be effective.

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1955 to 1960

There are many aspects to a characterization of psychiatry in the mid–20th century. In practice, there was little in the way of medication, much use of electroconvulsive therapy, excitement about psychoanalysis and psychotherapy, and a disparity between the relatively futile situation regarding therapeutics of serious psychiatric illness and the great investment of psychiatrists in working with neurotic people and increasingly with people with personality disorders. Certainly, in 1960, in training centers around the country, the highest calling was to go into psychoanalytic training. On the other hand, the stigma attached to psychiatry and psychiatric disorders was such that many students avoided telling their parents they were going into psychiatry.

Those were times when the notion of a continuity of psychological functioning was very much in the vanguard. That hypothesis meant that there were no clear boundaries between diseases. Diagnosis was given less attention. What little so-called objective clinical test data there were came from psychological testing. The brain was a mystery, and it was not the focus of attention by many academics, although as any number of the Freudian analysts would point out, Freud asserted that physical factors would ultimately explain a great deal of what he then described in psychological terms. Other means of testing were available, although they were of limited value. With regard to the brain, aside from psychological and ultimately neuropsychological testing, there were also skull x-rays, spinal taps, and pneumoencephalograms. But to the bulk of clinical psychiatry, these tests offered little.

Genes at that time were believed to play some role. The work of people such as Kallmann (1) had demonstrated that a number of psychiatric diseases showed increased frequency depending on the degree of familial closeness, but environmental factors were believed to have the main effect on psychiatric illness.

There was a pervasive and poisonous stigma attached to mental illness. Patients could not identify themselves as having psychiatric problems. Often practitioners—and even donors of funds—avoided saying too much about their psychiatric affiliation. The contempt of other physicians was dripping at times. Few well-known people acknowledged that they had a psychiatric disease.

This focus on environment included the hypothesis—subsequently discarded—that pathogenic parents could be held responsible for the development of schizophrenia. On the other hand, looking at what we knew about physiological factors, only three neurotransmitters were recognized: acetylcholine, epinephrine, and norepinephrine. Negative symptoms of schizophrenia were seen as inaccessible to treatment, even after some of the sedatives and ultimately some of the antipsychotic agents became available.

It was not unreasonable for people to set forth a lot of ideas with scanty if any data. Armchair philosophizing seemed to be in vogue. The epidemiology of mental disorders was only beginning with the Midtown Manhattan Study (2).

Psychiatrists rarely held positions

of any consequence outside the psychiatric field in general and academic medicine. Medicine and surgery, and perhaps pathology and pediatrics, dominated. There were few substantial psychiatric research centers other than the intramural National Institute of Mental Health (NIMH). A few academic centers were generating research, but not very many.

Psychiatric data were rare except in the field of psychopharmacology. Psychopharmacology has a long history of continuous focus on methodological and data-based attention to psychiatric issues and, as a result, has shown dramatic progress over the past four decades.

There was marked restriction in psychiatric reimbursement. As Jay Constantine, the chief staffer for Senator Huey Long, told me at one point, the barn door was closed, psychotherapy was not in, and that was the way it was going to be.

Psychiatric care was heavily inpatient. In 1960 there were 650,000 hospital beds. Other than private office-based practice, there was little outpatient work and almost no partial hospitalization facilities. Psychiatric facilities were often antiquated or flimsy compared with medical-surgical facilities, which affected decisions about allocation of resources for mental health services. Psychiatry was a field with diminished prestige and at times poorly justified enthusiasm about the potential of the latest therapeutic approach.

Today

So how are things today? Certainly, we have seen a vast buildup of academic departments and research facilities. Many academic centers have substantial research programs. Today NIMH is one of the government's great institutions.

Widespread attention is being given to the brain, and the preeminence or predominance of psychoanalysis is declining. Most programs recognize the fact that one has to have psychosocial, psychodynamic, and psychotherapeutic training along with training about biological factors in the brain.

By the year 2000, the numbers of chronic psychiatric hospital beds had shrunk to 57,000, and there was a rich proliferation of short-term general hospital units, outpatient services, and other alternatives to hospital treatment.

To get a picture of the richness of the scholarly work in psychiatric illness, it might be interesting to look at a sampling of current research focusing on some of our cardinal diseases. I want to commend the staff of the National Alliance for Research on Schizophrenia and Depression (NARSAD) for putting together some informative newsletters (from which I have drawn heavily) summarizing in a digestible form many of the recent research advances. Whereas there were some exploratory attempts in the 1960s to enable us to look at schizophrenia and contributing factors in the brain in an effective way, we were handicapped by the absence of tools. This situation has changed over the years, and the vastly improved research technology and greater sophistication of conceptual approaches have played a major role, leading to much more exacting and creative thinking about schizophrenia. Furthermore, there is more cause for therapeutic hope due to the demonstrated malleability of the brain, the recognition of new neuron development, and the expanded recognition of transmitter and receptor systems. Schizophrenia seems to be multiple diseases. A host of mechanisms may be involved. Many people and laboratories are working on a diverse group of brain factors, brain areas, and so on.

There were some exploratory attempts in the 1960s to look at schizophrenia and contributing factors in the brain in an effective way, but we were handicapped by lack of tools.

Today, we recognize more than 50 transmitters. The discovery of the importance of receptors in the middle of the century is being elaborated on. We know there are diverse kinds of receptors and that they have varied impact on the way drugs affect the body.

Many well-known people have publicly identified themselves as having a psychiatric illness, which has helped the field in a variety of ways. The NIMH research budget has grown dramatically; mental health research is integrated better into the field of medical research generally. The World Health Organization has said that neuropsychiatric disorders constitute the leading cause of disability worldwide, after communicable diseases. The neuropsychiatric disorders cause 11.5 percent of total disability. Also, WHO points out that unipolar depression will be the leading cause of disability worldwide by the year 2020.

The fact that neuropsychiatric disorders cause twice as much disability in developed countries as they do worldwide—25.1 percent compared with 11.5 percent—presents challenges to us. Are some disorders secondary to lifestyle—in other words, secondary to modern-day complex society and the result of stresses in the body and the brain? Are these disorders overdiagnosed in the developed countries? Or, rather, is it difficult to get reliable data from developing nations?

Among some patients with schizophrenia, there seems to be a genetic defect that manifests itself in late adolescence. Much tissue damage seems to have occurred by the time the illness manifests itself clinically. The notion of such early insults is linked to calls for early intervention. Wyatt (3), who also advocated such a focus, noted that combined psychosocial treatment with better antipsychotic medications may

make a big difference in treatment.

And yet psychiatric treatment has obstacles—some unique to psychiatry and some germane to all branches of medicine. One study in a review by Anne Brown (4) showed that of 32 new treatments added to the approved U.S. medications in 2001, only one was for psychiatric disorders—ziprasidone.

Each proven medication represents an average development cost of about $802 million. Very important is the frequency of a disease, which determines the extent of use of a particular drug and therefore the possibility that a drug company will recover its research money. There could be a danger if we find that, as diseases are disaggregated and subsets of diseases that affect smaller numbers of patients are identified, we are dealing with diseases for which the treatment does not have as wide a use. Such a scenario is economically unattractive to drug companies, as is the case with the various orphan drugs.

To introduce a new medication from the laboratory to the pharmacy takes ten to 12 years, the tail end of this period being 16.4 months, on average, for review by the Food and Drug Administration.

Despite these problems, the field of psychiatric research is rich with ideas and with clear evidence of progress. Today at least three drugs are used for bipolar disorder—lithium, tegretol, and valproic acid. They all affect inositol metabolism, and all seem to deplete inositol inside the neurons. The commonality of this effect is intriguing. Stanley Rapoport (5) has also found evidence of a role for lithium and valproic acid in the arachidonic acid cascade. The availability of multiple treatment alternatives fosters a potentially more productive examination of consistent physiologic effects from one treatment to another, which could help clarify the therapeutic mechanism.

In another line of research, a group of investigators from the Columbia University College of Physicians and Surgeons pointed out that the underdevelopment of glutamate-using neurons may cause an excess of dopamine-containing neurons that may lead to symptoms of schizophrenia (6). These and other researchers are putting forward much more elaborate and better-based hypotheses for the explanation of psychiatric phenomena than were previously available.

Another interesting line of work has been carried out by Freedman and associates (7), who are studying difficulties in focusing on relevant sounds and trouble with inhibitory neurons among persons with schizophrenia. These neurons use acetylcholine. In healthy humans, acetylcholine released from the midbrain affects the hippocampus to help the person focus. But among persons with schizophrenia, the type of acetylcholine receptor that is involved, known also as a nicotinic receptor, seems to go awry. The numbers of these receptors are reduced among persons with schizophrenia. Patients who chain-smoke seem to maintain the amount of nicotine in the brain at the right level to stimulate the alpha 7 nicotinic receptors. This phenomenon may account for the high frequency of chain-smoking among persons with schizophrenia, perhaps representing an effort to increase the number of acetylcholine receptors.

The field of psychiatric research is rich with ideas and with clear evidence of progress —for example, today at least three drugs are used for bipolar disorder.

Patients who are taking clozapine are less likely to chain-smoke. And clozapine is the medication that seems to normalize these receptors best. Also, in many cases of schizophrenia, there is a genetic link to the locus for this receptor. The gene is on chromosome 15.

Other links between loci on chromosome 15 and schizophrenia have been suggested. The link has been found in several different ethnic groups. People with schizophrenia may have trouble filtering out irrelevant information that could lead to symptoms such as auditory hallucinations (8).

Tsuang and colleagues (9) suggested a linkage between schizophrenia and genes on chromosome 13. Ken Davis and his associates (10) suggested an underexpression of myelination-related genes among persons with schizophrenia, possibly involving the oligodendroglia that produce myelin. Weinberger and colleagues (11) have been studying a possible interaction between two specific genes that increases the risk of schizophrenia. These genes are the COMT gene and a genetic variant of brain-derived neurotrophic factor (BDNF). BDNF regulates the growth of neurons and the neuronal component in diverse psychiatric disorders. The COMT variant seems to increase the risk of schizophrenia somewhat and affects human cortical function in the prefrontal region. A variant in the BDNF gene affects the hippocampal function in humans. It also may increase the risk of schizophrenia.

Given that prefrontal and hippocampal functional deficits have been observed in schizophrenia, interactions between these two brain regions in schizophrenia have been suggested. Weinberger's group found people with both COMT variant and BDNF met variant. The work of this group of researchers has suggested that such individuals have a significantly increased risk of schizophrenia. As Alan Brown (12) pointed out, this is the first evidence of an interactive effect between two specific genes, suggesting a possible genetic mechanism for prefrontal-hippocampal interaction in this disorder.

Beng Choon Ho and colleagues

(13) showed that although some patients with schizophrenia show an increased ventricular enlargement on magnetic resonance imaging (MRI) scans over time, not all of them do. Interestingly, patients who do show such enlargement have a poor outcome; this may be an important differentiating point between types of schizophrenia and certainly another point of entry into the study of the disease.

Judy Rapoport and associates (14) have shown impressive anatomic profiles of accelerated brain matter loss among persons with early-onset schizophrenia. The abnormality involves increasing amounts of cortex throughout adolescence. These researchers showed that the earliest deficits are in the parietal region related to visuospatial and associative thinking. Over five years, this progresses anteriorly into the temporal lobes in the areas of the prefrontal cortex and the frontal eye fields correlating with severity of psychosis and neuromotor, auditory, visual search, and frontal executive abnormalities. In temporal lobe gray matter, the loss was absent early but pervasive later.

Another interesting line of work is being conducted by Lahti and colleagues (15). They found that clozapine, in contrast to haloperidol, normalized the pattern of activation in the anterior cingulate brain area. This finding may explain the superior antipsychotic action of clozapine. Noteworthy is the fact that we are seeing various differentiations—that is, in treatment, diagnosis, and mechanisms regarding the way medications work and their results and effects.

Schooler (16) has looked at the differential value of treatments. She has used and recommends risperidone first rather than clozapine because it is associated with less-severe side effects. Importantly, white blood cell monitoring is not necessary. She also found that among people who continue to take risperidone, there is no difference in outcome compared with those who take clozapine.

Meltzer and colleagues (17) found that clozapine-treated patients, in contrast with those treated with olanzapine, showed significantly fewer suicide attempts and needed fewer rescue interventions and fewer hospitalizations to prevent suicide.

Roberto Sassi's group (18) have presented data supporting the idea that neuronal abnormalities in the prefrontal cortex of patients with bipolar disorders are present during the early stages of the disease.

DelBello and colleagues (19) have found correlations between bipolar disorder among adolescents and the presence of larger volumes of globus pallidus and striatum. Also, the male patients had lower prefrontal and thalamus volumes. These brain regions have been implicated in regulation of mood and attention.

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Carpenter and associates (20) stress yet another differentiation. They believe that the cause of illness differs at the level of genetic vulnerability to "deficit schizophrenia" (with negative symptoms) in contrast to "nondeficit schizophrenia." The relatives of patients with schizophrenia who have negative symptoms tend to be more socially isolated than those who do not have negative symptoms. Brain image findings also differ between these two patient groups.

Gur and colleagues (21) have shown that the difficulties in language, reasoning, memory, and attention faced by persons with schizophrenia—in other words, deficits in cognitive abilities that define us as humans—are evident at the onset of illness. Thus brain changes take place considerably before patients manifest their first symptoms of schizophrenia. Physicians should therefore be alert for cognitive deficits among young people who are at risk of developing schizophrenia. Early recognition might facilitate our ability to prevent or delay the onset of symptoms of schizophrenia.

Gur and colleagues also noted that patients try to overcome their cognitive deficits, but the earlier insult to the circuitry handicaps them. They point out that cognition is the best predictor of functional outcome and that a central challenge of current treatment is to go beyond the symptoms and target the cognitive difficulties. A growing literature suggests that atypical neuroleptics, such as risperidol, olanzapine, and clozapine, are more likely to ameliorate cognitive deficits.

Another fascinating area is paternal age as a factor in schizophrenia. Malaspina and colleagues (22) have shown an association between paternal age and increased risk of schizophrenia. They speculated that this elevated risk is due to the fact that male germ cells divide more often, which means that the frequency of mutations is increased. Additional risk factors include prenatal maternal malnutrition, obstetric complications, and infections in mothers.

In the general population, schizophrenia is present in one in 100 people. It is present in 10 percent of siblings of persons who already have schizophrenia. If an identical twin has the disorder, the second sibling's chance of having the disorder increases to 50 percent. Older paternal age is a risk factor in other diseases—for example, diseases associated with genetic mutations. Older age of the father is a factor associated with achondroplastic dwarfism, Marfan's syndrome, neurofibromatosis, and osteogenesis imperfecta. With complex disorders, such as congenital heart defects, neural tube defects, childhood brain cancer, mental retardation

of otherwise unknown etiology, Alzheimer's disease, and prostate cancer, there is also a paternal age effect.

The risk of schizophrenia doubles for children of fathers in their 40s compared with fathers who are younger. The risk is tripled in the case of men who are older than 50. The risk of schizophrenia approaches one in 80 children for fathers aged 40 to 45 and one in 50 for fathers aged over 50. Paternal age alone accounts for one in four cases in this population (22). Fathers with no family history of schizophrenia were on average 5.5 years older than those who had family members with the disease. Malaspina and colleagues are trying to define the characteristics associated with schizophrenia among patients with fathers over the age of 35.

NARSAD has both helped articulate and supported these and other exciting areas and directions focused on etiology, diagnosis, and treatment of psychiatric disorders. It is remarkable to think of the contrast in the nature and sophistication of the issues with which we are dealing today. Forty years ago, we were focusing on trying to refine psychotherapies for healthier populations and making do as best as possible with having psychotic patients traipse through the clinical system with its limited clinical and therapeutic capacity. At the time, we provided the best treatment we could with sedatives, hospitalizations—anything that would tide the patient over for the immediate situation—and sent people who did not remit to chronic care hospitals.

So we are in a remarkable period in which more and more exciting ideas, many different investigators and laboratories, and a richness of investigation and intellectual activity promise real changes in our understanding of psychiatric disorders. Of note too is the fact that many lines of research and many interesting mechanisms of disease are also important in nonpsychiatric illness, thereby inducing more interest and collaboration between research in different illnesses.

The future

What does that say for what the psychiatric agenda should be for those concerned about the field and—even more importantly—the patients being treated? I would say an agenda would include the following. First of all, the research needs to be as vigorous and well supported as possible. Second, we must ensure the development of a constant stream of young researchers. One of the big failings—not only in psychiatry, but in all branches of medicine—is the decline of numbers of people who are going into clinical investigation. Third, we should increase the focus on early detection. In the field of medicine, early detection seems to be valuable almost across the board, although its benefits obviously have to be examined and demonstrated for a given illness. But early detection of schizophrenia and perhaps early services for children who are at risk all seem to be valuable.

We must also focus our attention on parity. We have been making progress, but we are still not there. Whatever we can do to push that ball over the goal line, so to speak, is important. In addition, we need to press for adequate numbers of psychiatric beds and facilities. We must fight the reimbursement patterns to make psychiatric care economically feasible for providers, thereby reducing their reluctance to develop or sustain adequate services. We must fight efforts to segregate psychiatric facilities, as had been threatened in Vermont. Segregation is often a rationalization for less costly and inappropriate facilities.

In addition, we have to spread widely the recognition that psychiatric illnesses are far more treatable today. Such recognition should help what has already been a process of remarkable reduction in stigma. We also must encourage even more people who are competent, knowledgeable, and effective and who have had psychiatric illness to come out and make their situations public. Although the film *A Beautiful Mind* had its imperfections, one thing it did show was that someone as accomplished as a Nobel Prize winner can suffer from a psychiatric illness. We know there are many other accomplished people in the same situation, and the more psychiatric illness is seen as a disease no different from diabetes, hypertension, or heart disease, the better.

We also have to work at the bridge between biological and psychosocial treatments for an individual patient. That means not only the integration of treatment but also the integration of education—that is, the integration of clinicians and educators. I do not think there are enough professors who have the ability to weave their knowledge of psychosocial treatments and medical or biological treatments into a single presentation. We need teachers, educators, and researchers who can incorporate the linkage between these areas in their work.

We should also be retaining a certain skepticism about diagnosis. The diagnoses we have are at best approximations. As we accumulate more and more information that might help us understand basic etiology and mechanisms related to specific psychiatric illness, we will be able to organize our diagnostic systems more accurately.

In addition, we should be pushing as hard as we can to be firmly part of evidence-based medicine focusing on data and outcomes. Psychopharmacology has a long and very respectable history of evidence-based practice. We should make these practices part of all of psychiatry, which would place us squarely with the rest of medicine.

We should also heavily cross-fertilize psychiatric and nonpsychiatric research. The link between depression and cardiovascular disease and between depression and diabetes and stroke are indicative of this centrality of psychiatry to the approach to other illness. As much as internal medicine in the past decades has been central to most of the rest of health care and illness, psychiatry could—by virtue of the significance of brain and behavioral factors—be recognized for its high pertinence to much of health care. Psychiatry can also lead by creating good models for the relationship between biological and psychosocial issues.

Finally, psychiatry should focus heavily on the economic issues that link to the cost of mental health care. It has been a travesty that managed care and other reimbursement policies have battered down support for

psychiatric reimbursement as extensively as it has. We have to make a case for the complicated nature of psychiatric treatment and the value to productivity and healthy lives that good mental health care represents. Mental health treatment delivers a bang for the buck. Careful analysis as to how to affect high-quality care at best economic levels is invaluable.

Summary

The past 40 years in psychiatry have allowed a remarkable journey. To reflect back on the primitive nature of our field circa 1960 and to see where it has gone and how much good it can do is inspiring. Medicine—and psychiatry as a branch of medicine—has always been a marvelous field with a marvelous mission. We should be proud. As psychiatrists, we should represent the very best interests of the public and the highest concerns for patients. Those should be our top priorities and guiding principles.

The longevity of human beings has increased dramatically and so has the overall quality of life of people in the United States and around the world. We should continue that progress. If psychiatric illness is such a prominent cause of disability, we should make its treatment as effective, as patient centered, and as productive as possible. This may mean that 50 years from now, the nature of our understanding of the brain and behavior and of psychiatric treatment will have changed as dramatically as it has changed over the past 40 years. Such change may have an important effect on the duration and quality of human life. We will see people living into their 80s and 90s and even their 100s while experiencing less pain, less loss of function, and less indignity. That will result in a productive, happier population with a longer lifespan contributing to the national economy, as well as a more fitting valuing of the psychiatric and other medical professions that have played a contributory role to that dramatic change.

When I entered this field, I felt that psychiatry was concerned with people, with thinking, with social issues. It was potentially able to help. I feel those things even more today. We should look forward to sustaining the trajectory. We can give large numbers of people real help. We should work to enhance still further psychiatry's role as a critical part of our society for the benefit of our industry, our economy, and, most important, our people. ♦

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