

## Special Article

# The Social Construction of the Human Brain

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***Objective:** The purpose of this article is to review the development of concepts about the contribution of nature and nurture to brain structure and mental function, and to derive the implications of these changing concepts for clinical practice. **Method:** The literature of the past five decades, as refracted by the author's personal experience in academic psychiatry during that interval, is reviewed. **Results:** Psychiatric theory has swung through mighty arcs in recent years but has begun to re-equilibrate. Fifty years ago, psychoanalysis dominated the academic scene; for the past two decades, reductionist biological determinism has held the fort. Neither position is tenable. To subscribe to either is possible only by ignoring conflicting evidence. Worse, it means short-changing patients, whose disorders do not come neatly packaged into "organic" and "functional" compartments. Development is neither predestined in the genome nor completely malleable to shaping by the environment. Children inherit, along with their parents' genes, their parents, their peers, and the communities they inhabit. **Conclusions:** Contemporary psychiatric research conclusively demonstrates that mind/brain responds to biological and social vectors and is jointly constructed by both. Major brain pathways are specified in the genome; detailed connections are fashioned by, and consequently reflect, socially mediated experience in the world. Just at the time when integration at the level of theory is coming into sight, comprehensive patient care is endangered by for-profit corporate managed care, which is transforming medical visits into commodities on a production line. Physicians and patients must join in a coalition to protect quality, ensure access, and build continuity into all of medical care.*

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The central proposition of this article is that the human brain is constructed socially. This simple declarative sentence can be interpreted in two ways. The first is that concepts about brain and mind that are fashionable in a given era reflect the science and the politics of that era. The second, and more challenging, implication is that the cytoarchitectonics of the cerebral cortex are sculpted by input from the social environment because socialization shapes the essential human attributes of our species.

Many who will acknowledge that concepts of the brain reflect the state of the science of the day will deny that political values have anything to do with the matter. Yet, consider today's highly charged public dis-

course on whether mental diseases are biological or psychological; that is, whether they are "no one's fault" or "caused" by parents, spouses, or patients or by social disadvantage. The underlying quest among the families of the mentally ill is for moral exculpation. The fight between psychiatrists and psychologists about psychopharmacology is in part about hegemony over practice. Social biologists attribute the preponderance of mental disorders among the lowest socioeconomic-status quintile to downward drift; social activists assign it to the malign effects of economic disadvantage.

The claim that the fine details of brain anatomy are socially constructed may seem outrageous. Admittedly, this is an extrapolation from existing data. However, as Torsten Wiesel (1) has pointed out, "Genes controlling embryonic development shape the structure of the infant brain; the infant's experience in the world then fine-tunes the pattern of neural connections underlying the brain's function. Such fine-tuning . . . must surely continue through adulthood."

Few psychiatrists today would disagree that the brain

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is the organ of the mind. Two and a half millennia ago, that claim was bold. The Hippocratic author of *On the Sacred Disease* challenged popular superstition; the text indicted the ignorance and fraudulent practice of magicians and wizards who called epilepsy "sacred" (2). The cause of epilepsy, the writer asserted, lies in the brain:

Men ought to know that from the brain and the brain alone arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it . . . we think, we see, we hear, and we distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant . . . . By the same organ, we become mad or delirious, and fears and terrors assail us . . . and dreams and untimely wanderings . . . . All these things we endure from the brain when it is not healthy, but becomes abnormally hot, cold, moist, or dry, or suffers any other unnatural affection. (2, p. 344)

Delete "but becomes hot, cold, moist or dry" and the paragraph becomes altogether modern.

#### WHEN PSYCHOANALYSIS WAS IN BLOOM

In the 1950s and 1960s, however, few American psychiatrists had any interest in the brain. Psychoanalysis was in its ascendancy. When Leo Kanner (3) had brief quizzes on history given to some 300 psychiatric residents in programs across the country in 1954, the trainees proved to be far more familiar with Karl Abraham, Sandor Ferenczi, and Wilhelm Stekel (the latter a distinctly minor figure, even in the psychoanalytic pantheon) than they were with Julius Wagner von Jauregg, Daniel Tuke, or Jean Piaget. The brain had slipped below the psychiatric horizon. How had this happened? Why had psychoanalysis triumphed?

At the turn of this century, two exciting but competing developments each promised to clarify the nature of mental disorders. In the laboratory, the successes of bacteriology and pathology in unraveling the hidden core of general paresis aroused expectations of similar discoveries for the other psychoses. In the clinic, psychoanalysis attributed meaning to mental symptoms and proposed that they were best understood as the result of deviations in development.

However, dementia praecox and manic-depressive psychosis failed to yield to laboratory investigation. Neuropathology itself was discredited when report after report of histologic or bacteriologic abnormality proved to be an artifact or could not be confirmed. Therapeutic claims for prefrontal lobotomy proved false, and its practice scandalous (4). Genetics was captured by political ideology. Ernst Rudin, whom many continue to hail as the founder of psychiatric genetics, was an organizer of the Society for Racial Hygiene, served in Himmler's elite group to formulate the Nazi law for forced sterilization of the insane, and was awarded a medal in 1944 as a "pathbreaker in the field of human hereditary care" (5, 6). Nazi pseudogenetics was a caricature of genetic science, but it made many

psychiatrists of the 1950s unwilling to grant heredity any role in human behavior. Misuse continues. The epidemiology of HIV infection has been attributed to gene-based racial variation in sexual behavior (7) despite the patent absurdity of the claim (8).

Disenchantment with neuropsychiatry led to the abandonment of the search for brain pathology. Psychoanalysis, though it professed no role in the treatment of psychoses, made "sense" of psychopathology and opened a way to the ambulatory care of neurotic patients. Diagnosis and classification, the hallmarks of the medical approach, became almost irrelevant to clinical practice; psychotherapy, the principal mode of psychiatric treatment, dealt with individual and family psychodynamics rather than syndromes or diseases. Psychiatry made a virtue of the failure of its laboratory science. Whereas other medical specialists focused on organ pathophysiology because it provided the basis for designing specific remedies, psychiatrists were almost alone among physicians in listening to their patients, because that alone enabled them to diminish suffering.

Forty years ago, mapping behavior onto existing models of the brain was simply a nonstarter. Norepinephrine and acetylcholine were the only chemicals known to act at the synapse. The concept of the receptor had not yet been invented. The notion of "reuptake" and neurotransmitters was still in the wings. The millisecond time scale of neural events was far too fast for what was known of chemical kinetics; synaptic transmission was thought to be electrotonic. The conceptual nervous system was a static structure sprung forth fully formed at birth. We knew interconnections could be destroyed in the adult brain by disease or injury; little noticed was the demonstration by Rose et al. (9) of new fiber growth in the primate cerebral cortex after laminar destruction by alpha particles, despite its clear implications for a continuous process of remodeling. The conventional metaphor for the brain was a telephone switchboard. But who was the operator and where did she live? It was more convenient to proceed as if the central nervous system (CNS) was a black box and get on with the clinical work.

Psychoanalysis was virtually the only game in town. Its ideas were fun to play with; it attracted the brightest of the students. Theory was so constructed that disconfirmation was impossible. Criticism was entirely unavailing. The 1962 American Psychiatric Association (APA) Conference on Graduate Psychiatric Education concluded that "education in the fundamentals of psychoanalysis" is "an essential part of the general core curriculum" (10, p. 24), despite a solitary scorching attack on its predominance from the floor of the meeting (10, p. 8).

#### THE CHALLENGE TO PSYCHOANALYTIC HEGEMONY

Nonetheless, the tectonic plates underlying psychiatric phenomenology were shifting; an earthquake was

in process that would bring down its pillars. In the early 1950s, treatment of the psychoses was radically changed by a series of chance discoveries: of reserpine's psychotropic effects when it was used to treat hypertension; of chlorpromazine as a "tranquilizer" during research on anesthesia; of iproniazid as a euphoriant in treating tuberculosis; of the antidepressant properties of imipramine during therapeutic trials as a potential neuroleptic; and of the antimanic effects of lithium because its urate salt produced sedation in guinea pigs (11).

The new therapeutic armamentarium had major consequences for practice. It provided the means for aborting acute psychotic episodes and for minimizing recurrences. Because remissions could be induced in a relatively short time frame (and because insurance coverage became available), psychiatric units in general hospitals in the United States expanded rapidly (12). Because the new drugs were relatively syndrome-specific, diagnosis and classification, previously of concern to few American psychiatrists, became important clinical issues. The neo-Kraepelinian revival (13), inaugurated by Eli Robins and his Washington University colleagues *before* the era of psychopharmacology but accelerated by it, is reflected in the third and fourth editions of the APA Diagnostic and Statistical Manual of Mental Disorders.

These developments brought with them the peril that psychiatry might come to focus exclusively on the brain as an organ and overlook the experience of the patient as a person. Adopting a reductionist model of mental disorder promised professional respectability to a specialty hitherto denied legitimacy in the medical hierarchy.

Is this an overstatement? Recall the indiscriminating enthusiasm that greeted alleged "breakthroughs" in psychiatric genetics: reports of chromosomal localization of genes for manic-depressive disorder and for schizophrenia, "findings" that proved evanescent. Eight years ago, Egeland and co-workers (14) reported linking bipolar affective disorder in an Old Amish pedigree to two marker genes (the Harvey *ras* oncogene and the insulin gene) on the short arm of chromosome 11 by means of restriction fragment length polymorphisms (RFLPs). Two years later, that conclusion had to be modified; the calculated odds ratio shrank below statistical significance when the database of familial cases was extended (15). Sherrington et al. (16) reported linkage between schizophrenia and markers on chromosome 5 in heavily loaded British and Icelandic pedigrees; that, too, proved to be a false positive (K.K. Kidd, cited by Marx [17]). A similar fate has befallen alleged linkages between manic-depressive illness and markers on the X chromosome (18, 19) and between depression and the human lymphocyte antigen locus on chromosome 6 (20, 21). Linkage analysis by means of RFLPs in informative pedigrees is a powerful technique; its use with multiple markers without statistical correction of the odds ratios for repeated trials invites error (22).

## THE ADVENT OF MOLECULAR BIOLOGY

In contrast, progress in the molecular biology of gene-linked neuropsychiatric disorders has been quite extraordinary. The gene for Canavan's disease, a spongy degeneration of the brain, has been cloned; a missense mutation (a glutamine-to-alanine substitution) results in defective aspartoacylase hydrolytic activity and leads to a 200-fold increase in *N*-acetylaspartic acid levels in patients (23). The disease primarily affects Ashkenazi Jews; screening for Canavan's disease as well as Tay-Sachs disease may become a prudent public health measure. Tay-Sachs disease screening, premarital counseling, and selective abortion have reduced the incidence of Tay-Sachs disease in newborns among the Jewish populations of the United States and Canada by more than 90% over the past 25 years (24).

Fragile X mental retardation syndrome is an X-linked dominant disorder with reduced penetrance, 80% in males and 30% in females (25). It is associated with an expansion of the trinucleotide sequence CGG (26). In normal subjects, the number of repeats is polymorphic, varying from six to 52 copies. Nonpenetrant carriers exhibit "premutation" alleles of 52–230 repeats; affected individuals display from 230 to more than 1,000 (25). Female carriers generally have less severe clinical presentations than affected males and exhibit wide variation in phenotypic expression, which can include psychiatric manifestations (27). Mutation category determines the extent of the cognitive deficits in female carriers; whereas only one in three full-mutation carriers was of normal intelligence, all of the premutation carriers in the series of subjects studied by Taylor et al. (28) were in the normal range. Magnetic resonance imaging (MRI) and quantitative morphometry studies of patients with the full mutation have demonstrated increased volume of the caudate nucleus and (in males) the lateral ventricle (29). Earlier studies by these investigators had shown size deviations in the cerebellar vermis, fourth ventricle, and hippocampus.

Triplet repeats on other chromosomal loci have been found in myotonic dystrophy (30), spinobulbar muscular atrophy (31), spinocerebellar ataxia type 1 (32), and, most spectacularly, Huntington's disease (33). A worldwide study of 1,007 Huntington's disease patients from 43 national and ethnic groups revealed a characteristic CAG triplet repeated 36–121 times on chromosome 4. In the differential diagnosis of comparison patients with Alzheimer's disease, schizophrenia, depression, or other neurological disorders, the long repeat had a specificity of 100% and a sensitivity of 98.8% (34). It can now replace genetic linkage, which is a less accurate method and more limited in its applicability. Increase in the span of triplet multiplication accounts for the "anticipation" (the earlier onset and increasing severity of a disease as it passes through successive generations) noted clinically in many hereditary diseases (35). The CAG stretch on chromosome 4 is unstable during gamete formation and can change length; the larger the number of repeats, the earlier the onset of

Huntington's disease (36). Because two clinical phenomena associated with anticipation—greater severity and earlier age at onset—have been observed in successive generations in schizophrenic pedigrees, Petronis and Kennedy (37) have recently suggested that triplet repeats may account for the genetic transmission of this disorder. Now that methods are available for direct detection of triplet repeats (38), this hypothesis can be put to the test.

New discoveries in neurogenetics now reveal the relation between gene mutations and defects in neural structures. Each of the three major demyelinating forms of Charcot-Marie-Tooth (CMT) disease is associated with a different mutant gene, on chromosomes 1 (CMT1B), 17 (CMT1A), and X (CMTX1). In autosomal dominant CMT1A, the gene encoding peripheral myelin protein 22, laid down by Schwann cells, is abnormal (39). The clinical result is widespread loss of myelin, particularly around larger axons (40). In CMTX1, the mutations affect the gene for connexin32 (41–43). Connexins are a large family of proteins that make up the walls of gap junctions, the channels that extend across extracellular space and provide a privileged pathway for the exchange of small ions and second messenger molecules between cells. Connexin43 is found in astrocytes, ependyma, and the leptomeninges; connexin26 in pinealocytes, ependyma, and the leptomeninges; but connexin32 in the brain only, in neurons and astrocytes (44). However, many quandaries remain. CMTX1 can be severe and lethal; yet, at times, the disease manifests itself with late onset and relatively slow progression, a clinical finding difficult to reconcile with a fundamental flaw in gap junctions. Can other members of the family of connexin proteins, ordinarily not found in interneuronal gap junctions, “compensate” (45) for the defective connexin32 in late-onset forms of X-linked Charcot-Marie-Tooth disease?

In late 1992, Schellenberg and co-workers (46) demonstrated linkage to the long arm of chromosome 14 in several families with early-onset familial Alzheimer's disease, a finding confirmed and localized to 14q24.3 (47). Defects in this gene produce extensive amyloid plaque formation a decade earlier than mutations in the  $\beta$ -amyloid precursor protein gene itself (48). Great excitement followed upon the unexpected discovery that the  $\beta$ -amyloid peptide binds to apolipoprotein E, which plays a role in cholesterol metabolism in neuronal membranes and myelin sheaths (49, 50). Three common population variants of apolipoprotein E result from different alleles coding for single amino acid substitutions in the protein. Apolipoprotein E4 is preferentially enriched in Alzheimer plaques. Testing for the apolipoprotein E4 allele permits the identification of individuals in the population who are at fourfold increased risk for late-familial and sporadic Alzheimer's disease (51, 52); conversely, apolipoprotein E2 is associated with reduced risk (53).

Recent evidence suggests that the apolipoprotein E4 allele is associated with dementing forms of Parkinson's disease (54). No less intriguing is the recent suggestion

that the deposition of  $\beta$ -amyloid protein following head injury is more likely in individuals with the apolipoprotein E4 allele (55). Because positron emission tomography (PET) studies with [ $^{18}\text{F}$ ]fluorodeoxyglucose have demonstrated reduced metabolism in the frontal lobe of patients with Alzheimer's disease, Small and colleagues (56) investigated subjects with mild memory complaints who were at risk for familial Alzheimer's disease, both those who carried the apolipoprotein E4 allele and those who did not. The investigators found a significantly lower left parietal metabolism ratio and a higher left-right parietal asymmetry score in the apolipoprotein E4 carriers; their ratios and scores were intermediate between those of noncarriers and relatives with overt Alzheimer's disease. An exciting recent development is the success of Games and colleagues (57) in fabricating an animal model of Alzheimer's disease in transgenic mice that express high levels of human mutant  $\beta$ -amyloid precursor protein; the mice display cerebral  $\beta$ -amyloid peptide deposits, neuritic plaques, synaptic loss, and reactive gliosis, although they do not develop neurofibrillary tangles.

#### THE BRAIN BACK IN FASHION

The brain is back in fashion, and a welcome development that is! Some of us believed all along that the brain served as more than ballast inside the head to keep the skull from floating off into space (58, 59). Even more satisfying, the concepts of brain structure and function revealed by contemporary neuroscience accord with what is known about the development of behavior. We have learned about the luxuriant overgrowth of neurons and their processes in the course of development; activity selects survivors (60). If it is still the case that the basic ground plan is laid out in the genome, the precise neuroanatomic details are specified by activity-dependent competition between presynaptic axons for common postsynaptic target neurons (61).

Vertebrate neurons must interchange chemical stimuli with their targets to remain viable (62). Acetylcholine receptor-inducing activity is a 42-kilodalton protein produced in the neuron, which stimulates myotube differentiation as assessed by the expression of acetylcholine receptors (63). A family of neurotrophic factors supports neuronal survival (64); Mitsumoto and colleagues (65) have shown that ciliary neurotrophic factors and brain-derived neurotrophic factors, acting synergistically, can protect motor neurons against degeneration in wobbler mice, an animal model for amyotrophic lateral sclerosis. Glial-cell-line-derived neurotrophic factors rescue nigrostriatal (66) and mesencephalic (67) dopaminergic neurons, facial motor neurons (68), and developing motor neurons (69) from programmed and axotomy-induced cell death. A recent provocative discovery is that post-mortem human tissue from patients with amyotrophic lateral sclerosis reveals a marked decrease in ciliary neurotrophic factors in the spinal cord, most marked

in the ventral horn but also significant in the dorsal horn and column (70).

The competition between axon terminals and the feed-forward and feed-backward between presynaptic and postsynaptic cells shape and reshape ultimate cytoarchitectonic patterns (71). The role of protein synthesis in long-term memory and in enduring synaptic changes is now demonstrable. Long-term potentiation after high-frequency stimulus trains are delivered to the hippocampus has been posited as a model for long-term memory. Blocking gene transcription with chemical inhibitors abolishes the late phase of long-term potentiation (72). "Knockout" mice with lesions in those protein kinases that are associated with long-term potentiation in the hippocampus display relatively specific spatial learning problems (73).

The new technology in neuroscience makes possible a degree of precision in measuring localized brain activity in normal human beings that was altogether unimaginable just a few years ago (74). PET has demonstrated that different brain loci are in action during different types of working memory tasks (75, 76). An exciting recent finding appears to validate the belief that language functions have a different anatomic distribution in males and females. Using echo-planar functional MRI, Shaywitz et al. (77) have shown that brain activation during phonological tasks (but not orthographic or semantic tasks) is lateralized to the left inferior frontal gyrus in males, whereas activation occurs more diffusely in both comparable gyri in females. At an anatomic level, Schlaug and colleagues (78) have demonstrated that the planum temporale is larger on the left than on the right in musicians; the asymmetry is particularly marked in those with perfect pitch. Whether the size differential represents "hypertrophy" from use (as the finding in professional musicians might suggest), an inborn gift (as suggested by the data on perfect pitch), or both remains to be discovered.

## EXPERIENCE AND STRUCTURE

Because the species-typical environment, including the environment of the uterus, reliably supplies the input needed for the development of the CNS, CNS structures are as uniform as if they had been predestined in the genome (79). The visual system is a prime example. Genetically controlled mechanisms generate a coarse-grained topographic map; the fine-tuning of this map requires neural activity. Two specific instances are found in the formation of the ocular alternation layers in the geniculate nuclei and of the ocular dominance columns in the occipital cortex, the one process prenatal and the other postnatal. Initially, dendritic arborizations from both eyes intermingle. The formation of separate layers in the geniculate nuclei for each eye depends on spontaneously generated, asynchronous waves of electrical activity in the retinal ganglion cells (80). If spontaneous retinal electrical activity is abolished by tetrodotoxin, geniculate layers will not form (81).

In contrast, the formation of the ocular dominance columns in the occipital cortex requires that both eyes of the newborn receive precisely focused stimulation from the visual environment during the early months of postnatal life (the sensitive period). If one eye is occluded by an opaque cover, or if its acuity is blurred by a translucent cover, or if it is made strabismic by severing extraocular muscles, the unimpaired eye "captures" most columns in the absence of competition from the deprived eye (82). The change in the occipital cortex is irreversible if occlusion is maintained during the sensitive period; permanent change does not occur in the adult. If a kitten is reared in complete darkness, column formation is delayed and the sensitive period for monocular capture prolonged, but at the expense of diminished visual function (83). Deprivation need not be total; human astigmatism, if it is unrecognized and untreated, leads to permanent deficits in visual acuity in the abnormal meridional orientations (84). And it has long been known that amblyopia, in which there are incongruent visual images from the two eyes, results in permanent loss of effective vision from the unused eye in humans if the amblyopia is not corrected within the first 5 years of life. Cabelli et al. (85) have shown that the infusion of neurotrophin-4/5 or brain-derived neurotrophic factor, but not nerve growth factor or neurotrophin-3, into the primary visual cortex of a kitten inhibits formation of the ocular dominance columns. Neurotrophin-4/5 and brain-derived neurotrophic factor share a common receptor, TrkB. Therefore, investigators suggest that competition for limiting amounts of these neurotrophins may mediate activity-dependent axonal competition. Using the method of subtractive hybridization to identify genes that are overexpressed in cells in the kitten visual cortex versus comparable loci in adults, Prasad and Cynader (86) identified sequences coding for proteins involved in cell-cell interaction, remodeling, neurofilament assembly, neurotransmitter release, energy metabolism, RNA processing, and protein synthesis. This is a first step in dissecting the complex mechanisms that translate experience into structure.

Just as stimulus deprivation leads to anatomic as well as functional loss, enriched stimulation results in increased density of neurons and processes in the rat cerebral cortex (87). Synaptogenesis is keyed to learning (88). Rats reared for a year in a complex visual environment, in contrast to those reared in bare individual cages, show an increase in the depth and area of the superficial gray layer of the superior colliculus (89). Animals forced to learn motor skills (88) have a greater number of synapses per Purkinje cell in the cerebellar cortex than comparison animals forced to engage in the same total amount of rote motor activity. No less remarkable is the observation that early manipulation can attenuate the CNS deficits associated with aging in the rodent. Handling infant rats increases adrenal output and the concentration of glucocorticoid receptors in the hippocampus. This results in greater negative feedback in the adrenocortical axis and diminished glu-

cocorticoid secretion in response to stress. In consequence, rats handled in infancy show less neuronal loss in the hippocampus and fewer defects in memory as they age (90).

Activity-dependent competition underlies many of the phenomena seen in the developing visual nervous system (91). After even brief (6-day) monocular occlusion, geniculocortical axonal arbors reveal striking rearrangements; axonal branches bearing synapses respond quickly to changing patterns of neuronal activity (92). Gilbert and Wiesel (93) demonstrated marked changes in cortical topography in the adult animal within minutes after removal of afferent input to the visual cortex. Intracortical axonal sprouting of long-range laterally projecting neurons accompanies this topographic remodeling. "Terminal sprouting and synaptic proliferation represent the normal response of the adult cortex to extended modification of sensory experience" (94). Dynamic changes in cortical receptive field structures occur continuously during normal function.

The discovery that the adult brain is capable of extensive functional reorganization necessitates radical revision of traditional notions of anatomic fixity. In a study of adult women after mastectomy, Aglioti et al. (95) demonstrated the onset of sensory remapping as early as 6 days after surgery; phantom nipple sensations were evoked by stimulating skin regions near the amputated breast. Even more striking is the report (96) of the perceptual remapping of an amputated arm onto the face, including sensations of a carpal tunnel syndrome present in the hand of the patient before surgery! The patterns observed follow the sensory representation plot of the well-known Penfield homunculus (97). Studies using magnetoencephalography and MRI demonstrate that within weeks after surgery for syndactyly, the cortical somatosensory representation for the separated fingers expands rapidly because of their new functional status (98). As Posner (99) has phrased it, "If the neural systems used for a given task can change with 15 minutes of practice . . . how can we any longer separate organic structures from their experience in the organism's history?"

Candidate neurotransmitters number 100 and more—and still counting; more than 30 specific receptors at cell surfaces have been identified. The "coexistence" of transmitters in the peripheral nervous system has long been known; in the CNS, the opioid peptide dynorphin, present at a synapse also containing glutamate, modulates long-term potentiation in hippocampal mossy fibers (100). The acetylcholine-gated sodium channel has been characterized in exquisite detail. It is a transmembranous protein consisting of five subunits, the genes for each of which have been specified (101, 102); the electrical properties of each have been determined (103). Neurotransmitter release is by discrete packets released as quanta; that is, small synaptic vesicles contain equal numbers of transmitter molecules, which they release by exocytosis. Synapsin I, a phosphoprotein localized to those vesicles, regulates the number available for release by reversibly tethering

them to the actin cytoskeleton of the nerve terminal (104). Neurotransporters, which inactivate released neurotransmitters by reuptake, have been cloned for  $\gamma$ -aminobutyric acid (105), norepinephrine (106), and dopamine (107).

The most startling recent additions to the catalog of neural messengers are the gases, nitric oxide (108) and carbon monoxide (109). The enzymes necessary for their production, nitric oxide synthetase and heme oxygenase-2, have been localized in brain tissue. Nitric oxide and carbon monoxide are unique neurotransmitters in that they are not stored in synaptic vesicles but instead migrate by simple diffusion (110). We now know of neuromodulators, intercellular chemical messengers that produce relatively enduring changes in the responsiveness of synaptic elements by altering the properties of ion channels (111). Biochemically, the brain modifies its own responsiveness to incoming stimuli.

#### THE ONTOGENETIC NICHE

Nature and nurture stand in reciprocity, not opposition. All children inherit, along with their parents' genes, their parents, their peers, and the places they inhabit. West and King (112) coined the term "ontogenetic niche" to emphasize that development unfolds in an ecological and social setting that, like its genes, is species-typical for the organism. The ontogenetic niche is a legacy that structures development, a crucial link between parents and offspring, an envelope of life chances.

The early steps in the development of language are akin to the experience-dependent development of the visual system. All healthy human infants are born with the ability to learn language, an ability that is uniquely human; therefore, the potential, by definition, is specified in the genome. Children are able to infer grammatical rules from exemplars without ever being taught grammar per se. That, too, must reflect unique features of the human brain. However, the capacity to use grammar does not spring, like Minerva, fully formed from the head of Jove. Its acquisition and elaboration depend on social interaction. Whether a child acquires any language at all, let alone which specific language, is determined by the child's linguistic community. The degree of linguistic competence attained is a function of nature, nurture, and niche.

Auditory learning begins before birth. The human infant in utero hears its mother's voice repeatedly; on testing after birth, it is able to discriminate that voice from other female voices (113). Four-day-old French infants will suck harder in order to hear French instead of Russian because of in utero auditory experience (114). Young infants can detect differences between phonemes in all languages, including those that are not used in their native language. High-density EEG recordings of event-related potentials in 3-month-old infants identified a series of processing steps that accompany these discriminations (115). Presented with syllable strings

that were either identical or had one deviant, infants responded to the deviance with an electrophysiological change within 400 msec.

Within the first 6–12 months of life, however, in-born ability for universal phoneme discrimination is altered by experience, which “warps” the perceptual space underlying speech (116). Between 6 and 9 months of age, infants display listening preferences for sound patterns of their native language in lists of words they do not understand (117, 118). These language traits are most likely based on implicit (nondeclarative) memory (119). It is as if perceptual maps are “tuned” to native language (116). The older child, like the adult, is only able to discriminate the phonemes present in the language(s) it masters (120, 121). Japanese adults, unlike Japanese infants, cannot hear a difference between the English “l” and “r,” two sounds without an independent existence in the Japanese language. This is not the result of neural atrophy; rather, language-specific phonemic categories have suppressed nonspecific auditory sensitivity. The persistence of the capacity for discrimination between the sounds of the phonemes can be shown in carefully constructed nonlinguistic experiments (122). The notion that learning the mother tongue is localized to different neural circuits from those subserving second-language learning is supported by a report of paradoxical selective language recovery in a bilingual aphasic patient following subcortical lesions in the left basal ganglia (123). The patient could no longer speak her native dialect, whereas she was able to use the language she learned in school.

#### ACTION AT THE INTERFACE

The fact that psychopathology arises at the interface between the brain and social experience is evident from clinical investigations of disorders as varied as schizophrenia, depression, obsessive-compulsive disorder, and Alzheimer’s disease. Yet DSM-II, published in 1968, classified Alzheimer’s disease among the “psychoses associated with organic brain syndromes,” whereas schizophrenia and the affective disorders fell among the “psychoses not attributed to physical conditions” and obsessive-compulsive disorder among the neuroses—conditions psychiatrists considered to be entirely functional. Not quite 30 years later, all four disorders reveal the subtle interpenetration of psychosocial and biological factors in their pathogenesis.

#### SCHIZOPHRENIA

Is schizophrenia an inherited disorder? Any sober reading of the evidence warrants two conclusions. First, there clearly is a heritable component; second, heritability alone does not account for the observed variance. The risk among first-degree relatives of schizophrenic patients is some eight times higher than

the base rate in the population. The concordance for schizophrenia in pairs of identical twins is four to five times larger than that reported for same-sex fraternal twins (124). Such findings point unequivocally to heredity.

But there is a joker in the deck. Whereas the coefficient of genetic relationship between monozygotic twins should in theory be 1.0, the observed concordance for schizophrenia was about 0.31 among identical twins in a population-based study (125). Thus, the twin evidence points with equal force to an important role for nongenetic factors (126). The sensitivity of schizophrenia to the patient’s social environment is manifest from the impact of 1) institutionalization and 2) country of residence on the course of illness. I will consider each briefly in turn.

Textbooks refer to the “natural history” of schizophrenia as if the disorder were an autonomous entity following its own fate. To the contrary, the trajectory of every disease reflects the prevailing social conditions (including the availability and quality of medical care) at a given historical moment. What had been ascribed to the “nature” of schizophrenia as it was observed in large regimented asylums was shown to be the result of superimposing on the original clinical problem a chronic social breakdown syndrome (127). Administrative changes in institutional policy introduced in the decade after World War II under the label of “the open hospital” led to shorter stays and higher likelihood of discharge, changes that occurred well before the neuroleptic drugs were in widespread use (128).

The findings of the World Health Organization’s International Pilot Study of Schizophrenia (129) demonstrate marked differences in patient outcome between industrialized and developing countries. Prognosis 2 and 5 years after onset was considerably better in Agra, India; Cali, Colombia; and Ibadan, Nigeria than in developed countries (130, 131). In a second study, this time of patients entered into the protocol at first contact with a community agency, similar differences in outcome persisted (132). It is true that cases with acute onset, which display a distinctly better prognosis than those with insidious onset, are more common in the developing countries; nonetheless, prognosis is also better for cases with insidious onset in those countries. What accounts for these remarkable differences? It is tempting to suppose that they are attributable to “culture.” However, the manifest differences between the countries of the North and the South encompass such profound variations in housing, diet, education, work patterns, and disease exposure, as well as in beliefs and customs, that identifying the salient variables is a task still to be completed. As Jablensky and colleagues (133) pointed out, culture is not “a synonym for unexplained variance.” Future research designs must highlight the collection of data relevant to cultural differences, especially because “the enthusiastic embrace of new biological techniques in psychiatry tends to obscure the importance of the cultural context of psychiatric illness” (133).

## AFFECTIVE DISORDERS

The 1-year prevalence for affective disorders in the U.S. Epidemiologic Catchment Area study was 9.5% (134). Of the patients with depression, dysthymia, or bipolar disorder, only one-third received any treatment in the health care sector. When they did, that help was as likely to be obtained from a primary care physician as from a mental health specialist. How sick are those patients? In the Medical Outcomes Study of 11,000 primary care outpatients (135), patients who were depressed suffered as much disability and dysfunction as those with hypertension, diabetes, coronary artery disease, or arthritis; those with medical disorders and depressive symptoms were the worst off. There is an enormous public health burden of morbidity that manifests itself in primary care practice. The evidence indicates that it is not appropriately managed (136).

Depression is a chronic and disabling condition. A 2-year follow-up of the Medical Outcomes Study patients with major depression, dysthymia, or subsyndromal depressive symptoms (137) revealed a high rate of symptom persistence and a high probability of a major depressive episode at follow-up. A 5-year follow-up study of depressed patients attending psychiatric clinics (138) found that 12% had not recovered at all during that interval. The relapse rate after successful short-term treatment is disappointingly high (139). However, long-term drug maintenance plus supportive interpersonal psychotherapy at monthly intervals is effective in maintaining recovery (140). Beck and colleagues (141, 142) have shown that cognitive behavior therapy, directed at changing dysfunctional modes of thought in depressed patients, leads to rates of improvement as substantial as those produced by drug therapy, a finding that has been replicated by other groups (143, 144). At the same time, drugs modify the very psychological traits of depressed patients that cognitive behavior therapy was specifically designed to alter (144).

As with schizophrenia, the data on familial aggregation argue strongly for the genetic transmission of susceptibility to affective disorders; biochemical and endocrine abnormalities abound (145). But if the evidence for biochemical disorder is persuasive, so is the evidence for psychosocial disorder. Brown and Harris (146) documented the role of life events in precipitating episodes of depression. To what extent may the overlapping and sometimes contradictory findings on biological and psychological precipitants of clinical depression reflect "phenocopies" of a "genotype?" That is, is there validity to the old distinction between "endogenous" and "neurotic" depression? New and provocative data on this matter have recently been reported by collaborating groups in Pittsburgh (147) and London (148). Using the Bedford College Life Events and Difficulties Schedule with depressed patients, the investigators found that a significantly greater proportion of patients with "nonendogenous" depression had experienced severe life stress in the 6 months before the onset of their depressive episode. This held true despite the fact that

one group of investigators used the Research Diagnostic Criteria (RDC) and the other the Present State Examination (PSE) criteria for depression, and that the former used the American "endogenous" category from the RDC and the latter the British "melancholic/psychotic" category from the PSE. Among those classified in the London study as melancholic/psychotic, high scores on the Bedford College Life Events and Difficulties Schedule were very frequent in the interval before their first adult episode, whereas they were significantly less frequent in subsequent episodes (148).

Epidemiologic studies demonstrate secular trends in depression that defy genetic explanation (149). Across the many nations studied, there is a trend toward increasing rates of major depression over time at all sites. The data also show short-term fluctuations due to period and/or cohort effects, which vary considerably by site. There is speculation that political and economic disruptions may be correlated with changes in rates of depression (150).

## OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder is associated with changes in cerebral metabolism in the basal ganglia and limbic system and cortical projections from both (151). Serotonin reuptake inhibitors, on the one hand, and behavior therapy with exposure and response prevention, on the other, are effective in reducing symptoms of obsessive-compulsive disorder. When the patient improves, what happens to brain metabolism? Baxter et al. (152) used [<sup>18</sup>F]fluorodeoxyglucose PET to study the correlation between metabolic and clinical variables during treatment. The investigators contrasted patients who responded favorably to either drug or behavior treatment with patients who did not meet pre-established criteria for improvement. The responders to drug or behavior treatment displayed a significant reduction in glucose metabolism in the head of the right caudate nucleus, whereas the nonresponders and normal control subjects showed no change in successive PET scans. Two other investigations (153, 154) reported changes in metabolism after drug and behavior therapy, but the brain areas in the three studies do not correspond precisely. There is an obvious need for replication. If present evidence can be taken at face value, not only is psychopathology in obsessive-compulsive disorder associated with differences in brain function, but diminution of that psychopathology through treatment is associated with relative "normalization" of brain metabolism, whether the intervention is pharmacological or psychological. Do the brain changes initiate or reflect the psychological aberrations?

## DEMENTIA

No less evident is the role of psychosocial factors in Alzheimer's disease. Known risk factors for Alzhei-

mer's disease include trisomy 21 (155), head injury (156–158), and, as noted, the apolipoprotein E4 allele. At the same time, epidemiologic studies in countries as different as the United States, France, Italy, Sweden, Finland, Israel, and China (159) reveal a correlation between the amount of schooling received in youth and the prevalence of dementia in old age. A rather nice example of the schooling effect is provided by findings on cognitive impairment in two Australian cities, Canberra and Hobart (160). Mean Mini-Mental State examination scores in community surveys were higher in Canberra than in Hobart. However, all of the difference disappeared when the higher level of education in the Canberra elderly was taken into account. Furthermore, lack of formal education predicted decline in cognitive function in a 3-year follow-up of a community population aged 65 and over (161). If these findings are not merely an artifact of the way we test for dementia (careful analysis of the data suggests that it is not), the underlying mechanism may be that school-related intellectual activity results in an increase in synaptic density during development, just as a stimulus-rich environment does for other mammalian brains. The additional "brain reserve" may be responsible for delaying the appearance of clinical symptoms, even though the early pathological changes of Alzheimer's disease may be present. The higher educational attainment of Americans who will reach the age of risk after the turn of the century suggests that one cannot simply extrapolate from today's rates of Alzheimer's disease in planning for future service needs.

Thus, the evidence indicates that patients with depression, schizophrenia, obsessive-compulsive disorder, and Alzheimer's disease all exhibit problems of mind and brain, that changes in one alter the other, and that brain/mind responds to biological and social vectors.

#### THE RETURN OF THE REPRESSED

There can be no room for argument with the straightforward proposition that a functioning brain is a necessary condition for mental activity. Is it a sufficient condition? Guze (162) entitled his provocative address to the Royal College of Psychiatry "Biological Psychiatry: Is There Any Other Kind?" My answer is, Certainly not! But the same answer applies to the reciprocal question, the one Guze did not ask: Social psychiatry: is there any other kind?

Psychiatry is all biological and all social. There is no mental function without brain and social context. To ask how much of mind is biological and how much social is as meaningless as to ask how much of the area of a rectangle is due to its width and how much to its height or how much of the phenotype is due to genes (nature) and how much to environment (nurture).

However, at the very moment when the evidence for an integrated psychobiology has become compelling, the tentative union between psyche and soma in the clinic has come under severe stress from the exponential

growth in managed care. When cost control is elevated to the overriding determinant of corporate decisions, and medical visits are viewed as commodities on a production line (163), efficiency is gauged by the number of patients processed per unit of time, however destructive foreshortened consultations are to an ongoing relationship between patient and doctor. Managed care organizations ratchet down on the time allotted to visits and the number of visits permitted per illness episode. Psychotherapy is separated off from psychiatric as well as from general medical care, to be assigned to cheaper (at least for now!) providers and limited to homeopathic doses, whatever the loss to quality. The threat to primary care is no less than that to mental health services. The effectiveness of medical care can only be measured by long-term health outcomes in communities, not by lowering costs for treatment of episodic illness. Patients need time with their doctors. They need reason to believe that doctors place paramount emphasis on patient health rather than organizational profit; otherwise, they will not provide the intimate personal information needed for accurate diagnosis and appropriate treatment. Mutual responsibility for maintaining health requires sustained relationships with health care providers. Time is the currency of medical care; the population's health is the measure of its effectiveness. Physicians must take the leadership in defining standards for quality, availability, and continuity of care at a time when these attributes are at risk because of the overriding emphasis on the financial bottom line.

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