CHAPTER 2

Notes toward a Future History of Treatments for Cognitive Failure

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The history of treatments for cognitive failure falls into three broad areas. First, there is an early history, when claims for treatments that would now be termed "cognitive enhancing" and for putative treatments for dementia were much more common than many would now suspect. Second, there is a history determined primarily by events happening in the psychopharmacology of the functional psychoses. The dynamic of developments during this period aimed at conforming the domain of dementia to developments happening in the antidepressant field. Third, there is a more recent period in which both clinical and laboratory-based neuroscientific developments have begun to play more of a part.

The Early Period

The history of treatments for cognitive failure extends back at least as far as does the history of treatments for depression or psychosis. The nineteenth-century medical and lay literature featured advertisements for a range of compounds to treat the infirmities of old age and, in particular, what was termed senility. Indeed, such ads were much more common than ads touting a cure

for frank mental illness. In the early twentieth century, a range of compounds including the classical stimulants such as dexamphetamine and methylphenidate crept into use for this purpose alongside a group of drugs termed "analeptics," which included metrazole and even strychnine in low doses. This use appears to have been on the simple basis that every effort should be made to "stimulate" any remaining cognitive function to its maximum.

In the 1950s and 1960s, against a backdrop of interest in arteriosclerosis, there was an increasing emphasis on the role of brain vascular disease as a cause of cognitive decline in old age. This led to the introduction of a group of treatments aimed at enhancing cerebral blood flow and to claims that drugs already in use had such flow-enhancing properties. Drugs such as dihydroergotamine (Hydergine), nicergoline, cyclandelate, and naftidrofuryl came to be widely advertised and used for this purpose. None came with the kind of clinical trial evidence that would now be needed to introduce a drug on the market.

With the eclipse of the vasodilator theories, in the 1970s, Hydergine was reinvented by Sandoz as a cerebral metabolism enhancer: "The old belief—that mental deterioration in the elderly is caused by impaired blood supply to the brain—has been exploded. A report in the *Lancet* reviewing world wide published evidence concludes that atherosclerosis does not cause mental deterioration and that the term 'cerebral arteriosclerosis' is inaccurate and should not be used in this condition. The only rational way to reverse insidious mental deterioration is to treat the real defect at source. Hydergine does precisely that. Hydergine acts directly to improve cerebral metabolism" (Sandoz 1970).

The vast majority of vasodilator, cerebral metabolism enhancer, and stimulant drugs used for senility were swept away in the 1970s as part of the Drug Efficacy Study Implementation (DESI) program instituted after the 1962 amendment to the Food, Drugs, and Cosmetics Act. Following the 1962 amendment, the U.S. Food and Drug Administration (FDA) was charged with establishing not only whether new drugs worked but also whether drugs currently on the market were effective in addition to being safe. This led to the creation of a number of efficacy panels made up largely of scientists with links to the National Academy of Sciences. These panels ruled on more than 3000 compounds based on the published study data. A majority of the psychotropic compounds reviewed were adjudged by the psychiatry panel not to have a strong evidence base in terms of controlled trial data, but nevertheless to have considerable evidence of efficacy. Companies sponsoring these drugs had the

opportunity to undertake further studies, but in the case of drugs off patent, most companies chose not to do so. Unless compounds were determined to have a clear evidence base, the FDA removed them from the market, in many cases despite considerable evidence of efficacy (Shorter 2002).

Retrospectively, the case for Hydergine looks strong (Schneider and Olin 1994). In the case of metrazole, another drug eliminated, the manufacturers protested and took their action to the Supreme Court, where, in *Weinberger v. Bentex,* which was decided on June 18, 1973, a decision confirmed the authority of the FDA to withdraw such drugs. It seems likely that a number of important therapeutic leads may have been lost as a result of this clearing out of the therapeutic armamentarium.

The Concept of a Nootropic

The consequences of this clearout were felt in the conceptual as well as the therapeutic domain and led to the paradox of a new development that already feels more part of a distant history than some of the notions it sought to replace. In the 1960s, the psychotropic marketplace looked very different from what it looked like at the end of the century. It was dominated by broadly stimulant or sedative compounds that would not readily be classified as anxiolytics, antidepressants, or antipsychotics and by concepts of nervous disorder such as senility and nervous breakdown. The notion of a tranquilizer came into being only in the mid-1950s, and while it was immediately popular, the word "antidepressant" does not feature in popular dictionaries until the 1980s (Healy 1997). A number of neologisms, such as "neuroleptics" and "thymoleptics," were conjured up to account for the effects of drugs like chlorpromazine and imipramine. The pharmacological revolution of the 1950s and 1960s called forth new conceptual developments of this sort, one of which was the concept of a nootropic.

The term "nootropic" was coined by Corneliu Giurgea, a Romanian who had trained in psychophysiology in the Soviet Union and later became director of research at UCB Pharma in the late 1960s on the back of the development of piracetam (2-oxo-pyrrolidone) (Giurgea 1973). Originally developed to combat motion sickness in 1964, piracetam appeared in animal tests to promote learning and prevent hypoxic-induced amnesia. By 1972, there were already 700 papers on various aspects of piracetam's profile. The key features of a nootropic were that it would promote learning as well as enhance resistance of learned behaviors to disruption by stressors like hypoxia, barbitu-

rates, and scopolamine. Such compounds, it was intimated, would increase cerebral "tone" and would be almost completely lacking in conventional psychotropic side effects. These were drugs that would forestall senility rather than agents that would treat an established dementia.

A range of compounds followed piracetam into the nootropic stable—pyritinol, centrophenoxine, aniracetam, pramiracetam, oxiracetam, and idebenone—sparking a great deal of basic animal research in laboratories from Venezuela to Poland. Many of these compounds came on to the market in European countries. Claims have been made that piracetam is effective in alcohol withdrawal (Skondia and Kabes 1985) and in dementia or other cognitive impairments (Chouinard et al. 1983; Croisile et al. 1993; Platt et al. 1993). But no nootropic has ever made it to the U.S. market.

Biochemically, the demonstrated effects of piracetam in the 1970s and 1980s were also exciting; it reduced lipofuscin accumulation in the brain and reversed the effects of both anticholinergics and protein synthesis inhibitors. Demonstrations of enhanced cholinergic function on combinations of piracetam and choline or lecithin in animals (Bartus, Dean, and Beer 1981), and in patients with dementing disorders (Ferris et al. 1982; Smith et al. 1984) helped the emergence of a cholinergic hypothesis of dementia in the 1980s, and this hypothesis in turn helped to maintain interest in piracetam and other drugs in this group. With the emergence of interest in glutamate, a flood of articles demonstrated clear effects of piracetam on glutamatergic systems.

Both piracetam and the very concept of a nootropic have, however, disappeared. A multipotent, side-effect free agent was perhaps too good to be true, but there remain three aspects of interest to the piracetam story. First, piracetam, and the notion of a nootropic, function almost as a Rorschach test for the field of cognitive enhancement in general. Almost every neurotransmitter system, most degenerative disorders, and a variety of conditions unresponsive to other therapies found a home under the nootropic roof at one point—or put another way, were colonized by this conceptual virus (meme). Second, a great deal of solid research on protein disruption, or protein synthesis enhancement, through to research on cholinergic systems in the 1970s and 1980s was done under the nootropic banner. Clinicians and basic researchers saw themselves as working in the nootropic field, in just the way that other researchers saw themselves as working on antidepressants or neuroleptics. And finally, the concept of nootropic arguably survives in the popular notion of a smart drug.

The Middle Period

The Chlorpromazine Watershed

The introduction of chlorpromazine in France in 1952 and in the United States in 1955 changed mindsets regarding the pharmacotherapy of psychiatric disorders. It ultimately led to the introduction of the notion of a lesion that drug treatment might correct. To appreciate the significance of this, one must recall that there was little or no understanding of the possibility of chemical neurotransmission at the time and as such no basis for a lesion that chlorpromazine might rectify. In the case of chlorpromazine, this new understanding was ultimately formulated in the 1970s as the dopamine hypothesis of schizophrenia, which postulated defective dopaminergic neurotransmission that neuroleptic therapy corrected.

It took a great deal of neuroscientific development, however, for such an idea to catch hold. Only in the 1970s did the treatment of schizophrenia, for example, become supposedly rational in this sense. Before that, the use of the antipsychotics or neuroleptics was largely for behavioral disturbances or for symptomatic use. Many advertisements featured the use of the neuroleptics for senile disturbances of behavior, for example.

At the same time that chlorpromazine was introduced, a range of investigators noted the effects of isoniazid and iproniazid on the mental states of tubercular patients (Healy 1997). From this set of observations, the antidepressant class of drugs were developed. Iproniazid in particular was proposed early on to work by virtue of being a monoamine oxidase inhibitor (MAOI), supposedly increasing cerebral monoamines. This notion led directly to the most influential lesion theory—the catecholamine hypothesis of depression (Schildkraut 1965).

This theory, which appeared eminently rational at the time, retrospectively appears no less mythological than the notion that Hydergine might be a cerebral metabolism enhancer (Healy 1997). There were, in fact, always good grounds to doubt the theory. For instance, isoniazid, which appears to be an effective antidepressant (Salzer and Lurie 1955), was known not to be an MAOI. Furthermore, when iproniazid, which was an MAOI, was removed from the market because of liver toxicity and replaced by isocarboxazid, also an MAOI, the new drug simply didn't seem to work well (Kline 1970). Finally, iproniazid, unlike subsequent MAOIs, in high doses appeared to cause psychosis. This indicates that iproniazid may have significant actions on systems

other than the monoamine systems. If isoniazid and iproniazid do not have effects in common with other MAOIs on catecholamine or serotonergic systems, it remains entirely possible that they have common effects on glutamatergic or other systems.

There are further lessons to be learned from the MAOI group of drugs. The discovery of their antidepressant effects stemmed essentially from a capitalization upon their side effects. For instance, these drugs caused weight gain when used in tuberculosis, so it seemed like a good idea to try them out on depressed patients, who commonly lost weight. However, the new focus on catecholamines and serotonin, as a result of the supposed biochemical effects of the MAOIs, brought with it the notion that the primary effects of the drugs were biochemical. These new biochemical side effects were unlike any previous side effects of treatment—they were ideological side effects rather than the real thing.

For instance, as depression came to be seen as a disorder involving a monoamine lesion, then the anticholinergic effects of early antidepressants were transformed pretty much by definition into side effects. A generation of textbooks noted that these anticholinergic side effects included blurred vision, urinary retention, and cognitive disturbances, particularly memory disturbances, all of which were problems that would be done away with by the creation of more selective norepinephrine or serotonin reuptake inhibiting drugs. It took thirty years for the established wisdom to be overturned by the example of urinary retention in antidepressants such as reboxetine and duloxetine, which were norepinephrine reuptake inhibitors devoid of effects on cholinergic systems. But arguably such ideas should never have developed in the first instance, as the same clinicians who talked about anticholinergic problems such as urinary retention were regularly treating patients with much more potent anticholinergic antidotes to neuroleptic-induced parkinsonism, without any resulting urinary problems. Neuroscience was beginning to lead rather than follow clinical observation.

As what might be called a "side effect" of this process, a premium was put on the notion that acetylcholine (ACh) might be the neurotransmitter involved in Alzheimer's disease. The proposal that ACh might play a role in dementia stemmed from two sources, one of which was a linkage between anticholinergic drugs and amnestic effects. But a second, and at least as important, source was the fact that few neurotransmitters were known to exist in the body, and as serotonin and noradrenaline had become parceled out among the mood disorders, and dopamine was implicated in schizophrenia, this left only one

neurotransmitter, acetylcholine, to play a role in the dementias. By the 1970s, early speculation began to implicate acetylcholine in dementia, and this was supported by findings of cholinergic changes in dementing brains, leading by the early 1980s to a range of articles proposing a cholinergic hypothesis of dementia (Bartus et al. 1982; Davis and Mohs 1986). This development ran counter to centuries of clinical observation in that excessive dosing with drugs—now known to be anticholinergic—had traditionally been linked to delirium rather than dementia.

The Cholinergic Hypothesis of Dementia

The cholinergic hypothesis led to a focusing of efforts on the production of drugs that would enhance cholinergic function, reversing a presumed deficit of cholinergic function in dementia. The first drugs of this sort included agents like choline and lecithin, which were aimed at replacing deficiencies in acetylcholine levels, in much the same way that L-dopa reversed the effects of Parkinson's disease. Some early results suggested beneficial effects of these treatments, especially when combined with nootropic agents such as piracetam. A subsequent generation of drugs aimed at inhibiting the breakdown of acetylcholine by its metabolizing enzyme cholinesterase. These early cholinesterase inhibitors included tetrahydroaminoacridine (tacrine) and later pyridostigmine.

The tacrine story has been outlined in detail elsewhere (Leber 1996). In brief, early reports in 1983 (Summers et al. 1986) suggested that tacrine had an awakening effect on Alzheimer's dementia comparable to the use of agents such as L-dopa for Parkinson's disease. Efforts to replicate this early work proved unsuccessful. However, tacrine quickly ended up being used widely off label, despite the fact that this drug had little toxicity data available to indicate whether such use would be safe. Subsequent efforts to demonstrate the efficacy of tacrine were unsuccessful (Leber 1996), but by this time a clamor for the licensing of tacrine had built up so that it was all but impossible not to license this drug. Once licensed, tacrine failed to have any clear impact clinically other than on the development of a greater number of memory clinics and the creation of an expectation that a new generation of specifically antidementia drugs would emerge in due course.

The development of tacrine spurred interest in the cholinesterase inhibitors, which ultimately led to the licensing of donepezil, a drug developed by Eisai and licensed by Pfizer, followed by rivastigmine and galantamine. The

fuss around tacrine also played a key part in the emergence of these drugs and their subsequent marketing in another way. In an effort to cope with the problems of efficacy assessment that tacrine posed, the regulators and a range of interested clinicians set about developing standards by which antidementia drugs might be recognized. The new standards included statements of the size of a treatment effect on instruments such as the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). These standards later permitted the licensing of drugs such as donepezil, even though the apparent treatment benefits, at least when judged across groups of patients with dementia, were minimal.

The early years of the rising popularity of the cholinesterase inhibitors were a time of concern for some, who worried that the extensive use of these drugs would potentially bust health care budgets, considering the scale of the clinical problem, the cost of the drugs, and the expectations that had been engendered. However, the actual adoption in most countries has been far more modest. Given indicators of an extensive use of stimulants among elderly people in the 1940s, 1950s, and 1960s, the rate of use of cholinesterase inhibitors may in fact not have been substantially different from the use of stimulants for elderly people in a previous generation.

By the mid- to late 1990s, a further feature of this marketplace was an almost exclusive focus on the treatment of Alzheimer's dementia, where the previous focus had been on the management of cognitive decline or the treatment of cognitive failure. By the late 1980s, most dementing disorders had been subsumed under the heading of Alzheimer's dementia and, aside from the use of aspirin, the notion of managing a cerebrovascular input to the clinical picture had been all but precluded. During this period, multi-infarct dementia had, rhetorically at least, all but ceased to exist.

The Recent Period

Enhancement or Cure?

While the formal selling of selective serotonin reuptake inhibitors (SSRIs) was constrained within a disease and lesion framework—"to correct the chemical imbalance known to be involved in these disorders"—the failure to find a lesion opened up the possibility that aminergic drugs enhanced certain cerebral functions and that this enhancement could be more or less helpful in certain disorders. If this was the case, it was also possible that these drugs might also have an effect in nondiseased states.

The initial conceptual basis for psychotropic drug use in fact included the possibility that these agents might have an effect on nondiseased states. Before chlorpromazine, the potential effects of psychotropic agents were framed within dimensional models of personality such as that put forward by Eysenck (Eysenck 1952; Claridge 1969; Healy 2002). Theories such as Eysenck's proposed that people vary on axes such as introversion and extraversion and that, for example, stimulants and sedatives can affect introverts and extraverts differently and that these differential effects are grounded in genetic/constitutional factors.

The use of the antipsychotics and antidepressants through the 1960s led to a gradual eclipse of this line of dimensional thinking and the emergence of much more categorical views of mental illness, best enshrined perhaps in popular notions that the *Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition (DSM-III) embodied a revival of Kraepelinian thinking, when in fact the new focus on syndromes arguably owed much more to Adolf Meyer than to Kraepelin. Dimensional ideas, though, persisted as a subterranean stream within the modern era. This stream resurfaced at certain points, as, for example, in the suggestions in *Listening to Prozac* (Kramer 1993) that Prozac could make even people who might not be ill better than they had been, that it enhanced functions. Such an action is most parsimoniously viewed in terms of Prozac having effects on a dimensional spectrum so that certain ingrained features of particular personalities change, allowing some people who take it to become better than well.

There is a considerable amount of evidence that selective noradrenaline and selective serotonin reuptake inhibitors indeed have effects on functional aspects of personality and different effects on different personality types (Tranter et al. 2002; Healy 2004). Furthermore, in contrast to the supposed anticholinergic side effects of antidepressants, for centuries anticholinergic agents such as mandragora and henbane, and later hyoscine, had been used to treat nervous problems; they helped calm patients and gave a euphoric sense to many (Healy 2002). Indeed, a series of early controlled clinical trials suggested that atropine might be beneficial in melancholic depression (Hoch and Maus 1932; Herz 1965; Loew and Taeschler 1965; Kasper, Moises, and Beckmann 1981). But for a variety of reasons, probably primarily to do with patents, no modern pharmaceutical company has seen fit to develop agents of this kind, and as popular awareness of the traditional origins of these drugs vanished, it became easier to brand the anticholinergic effects as side effects. As the efficacy of anticholinergic agents in nervous states would not now lead

to a cholinergic-deficit theory of depression, these results might best be reconceptualized in dimensional or functional terms.

Early research on antidepressants gave rise to an orthodox view of how catecholamine and serotonin systems function. In contrast, through the 1960s, an effort to produce more selective MAOIs led to the development of monoamine oxidase-B inhibitors and the development of drugs such as deprenyl by Joseph Knoll and colleagues (Varga and Tringer 1967; Knoll 2000). The use of deprenyl in particular led to a recognition that underneath the traditional economy of the catecholamine system lay a group of catecholamine-release-enhancing mechanisms. These appeared to be much more finely tuned physiological mechanisms than reuptake processes; they are the mechanisms that are called into play, for example, when animals are in situations of extreme stress, such as when a hare finds itself the likely victim of an attack by an eagle. In such situations, the animal must mobilize its resources with extraordinary rapidity and must achieve a superoptimal level of functioning if there is to be any chance of escape.

Considerations of this phenomenon led Knoll to posit a theory of active reflexes (1969), which stood at odds with then dominant Pavlovian theories of conditioning. Hand in hand with the development of this theory, Knoll began to focus on the catecholamine-release mechanism and to develop drugs more selective to it. A combination of drugs selective to this mechanism, experiments on these drugs, and an emphasis on active reflexes led ultimately to the proposal by Knoll among others that Parkinson's disease, Alzheimer's disease, and other degenerative diseases might be manifestations of an aging process rather than discrete diseases in their own right and that agents active on monoamine-release mechanisms, by enhancing the economy and efficiency of the organism, might forestall aging and minimize risks of developing degenerative disorders (Knoll 2003). There appears to be considerable evidence from animal studies that, for example, aspects of aging can be delayed by agents such as deprenyl. Deprenyl in turn became an agent aimed at forestalling the progression of Parkinson's disease. Whether such a drug might have had a comparable effect on Alzheimer's disease remains uncertain in the case of deprenyl and untested in the case of other compounds in this group (Sano et al. 1997).

The prospect of such an effect raises a number of questions. Is forestalling aging an example of enhancement or a treatment of a disease? Drugs that might prevent disease by delaying an aging process furthermore face a critical problem in terms of their development, which is that the structure and regula-

tion of the current marketplace would require a demonstration of a preventative effect on a pathology that might otherwise appear. Such a demonstration would require holding a large number of subjects in a clinical trial program over a long period of time. This would involve a much greater scientific effort and financial outlay than drug companies have been used to hitherto. Current FDA models, which license drugs on the basis of two well-controlled trials, permit the economic development of antidepressants of the type we've had but do not sit readily with the licensing of agents that might be preventative.

A New Neuroscience: Glutamate

At much the same time as the monoamine hypothesis of depression was taking shape in the 1960s, awareness had developed that the brain had components such as glutamate and GABA, and in fact these were present in the brain in much greater quantities than the catecholamines, serotonin, or acetylcholine. This was a time, however, when the notion of chemical neurotransmission itself was first proposed and was not generally accepted. In the 1960s, no one was prepared to concede that glutamate was a neurotransmitter.

The preliminary work, which demonstrated the role of glutamate in the cerebral economy, came from Jeff Watkins, a chemist who had left Australia and done undergraduate and postgraduate work in England and later at Yale. After John Eccles, the famous neurophysiologist, moved back to Melbourne, Watkins applied to join his laboratory. Part of Eccles's fame stemmed from the fact that he was the most celebrated convert from the group of scientists who had espoused an electrical theory of neurotransmission in preference to a chemical theory.

While working in Melbourne, Watkins and a colleague, David Curtis, took a simple approach toward the question of mapping further neurotransmitters in the brain. They began with chemicals that could be found on the laboratory shelf. One of these was glutamate, which applied from the laboratory jar appeared to act as though it were a neurotransmitter (Watkins 1998).

Several difficulties stood in the way of recognizing what had been discovered. One of these was the continuing bias against the notion of chemical neurotransmission. A second was the disbelief that a chemical present in such great quantities in the brain might be a neurotransmitter. A third and perhaps more pressing problem was that there were no apparent drugs that could manipulate this system, and without such agents it was difficult to know whether this discovery had any functional significance.

The following two decades led Watkins, and growing numbers of scientists interested in glutamate, to map out the new system, to discover its receptors, and finally to help isolate drugs that manipulated glutamate functions. It transpired that the glutamate system had a number of receptors, of which the most famous has become the NMDA receptor. This is a hugely complex receptor system that has multiple sites, in particular a site that binds glycine. A variety of agents can act on the different components of the site, both directly on the ionic channel in the receptor and indirectly by modulating entry to the channel or through changes to the channel structure itself. Ions such as magnesium and zinc are needed as co-transmitters. Furthermore, it has become clear that the NMDA receptor comes in a number of different forms. There is a form that would now be thought of as a classical receptor, which is an ionophore that permits a flow of ions through it, and a further group of receptors called metabotropic receptors (Parsons, Wojciech, and Quack 1998).

The first evidence that there might be drugs that could act on glutamate offered a gloomy glimpse of the future. It appeared that such drugs, which included phencyclidine and ketamine, caused psychosis. In short order, drugs acting on the glutamate system became associated with a triggering of both psychosis and convulsions. The incentive to continue research in this area, however, lay in accumulating evidence that the glutamate system is linked to neurodegenerative processes and that most excitotoxic agents appear to act on the glutamate system (Olney 1992).

The key to unlocking a range of drugs that would act more safely on the glutamate systems lay in two sets of developments. One was the recognition of metabotropic receptors, which act to modulate the system rather than acting directly on it. The drugs with problematic effects were ones that acted directly on ion channels. The second was to recognize that a great number of drugs that were then in use, which had not been developed as agents to act on the glutamate system, did in fact act on that system. The mistake had been to attempt to devise agents genetically specific to the receptor system—an approach that might be regarded as a physician's approach to the issues. It was better to take a surgeon's approach it seemed—look for something that did in fact work rather than something that should in principle work (Watkins 1998).

Awareness grew that a number of agents had effects on the glutamate system. Some of these had low affinity effects on the channel, such as the antiviral agent amantadine, or memantine, an agent developed for glucose regulation, or the analgesic dextrophan and the anticholinergic drug orphenadrine (Parsons, Wojciech, and Quack 1998). Haloperidol is a selective NMDA antago-

nist, and the antitubercular agent d-cycloserine is a glycine partial agonist. Indeed as mentioned above, the original antitubercular psychotropic drug iproniazid, which was known to cause psychosis, may also have effects on this system. The effects of iproniazid and the comparable anxiolytic effects of d-cycloserine open up the question of whether the glutamate system is primarily involved in degenerative disorders or whether it might have a broader psychotropic role.

Memantine, having first been developed as a glucose stabilizer in the 1970s by Lilly, crept into use in Germany primarily as a tonic for older people. Through its use as a tonic, awareness developed that it might potentially have beneficial effects in preventing neurodegeneration. This led to an increasing use of the compound in dementing conditions and sufficient evidence that it had beneficial effects in these conditions to permit its development as a treatment for dementia. However, it remains unclear whether this drug actually interferes with the disease process, and is therefore delaying the progression of the disease, or whether it has some unspecified functional effect that shows up beneficially in patients who have neurodegenerative disorders. Other agents active on the NMDA system, such as cycloserine for example, appear to be effective anxiolytic agents.

Cognitive Rigidity and Other Prodromes

The end of the twentieth century also brought a return of interest in the possible cerebrovascular basis for cognitive failure. There was an increasing awareness that many apparently normal individuals over the age of 50 show extensive lacunar infarcts. There is every reason to believe that "small" vessel disease (Cummings 1994; Kramer et al. 2002) might underpin cognitive failure in a broader sense than Alzheimer's dementia. It seems highly likely, for instance, that such changes underpin the physical rigidity or infirmity of old age. There seems little reason to think that they might not also underpin wider cognitive changes, such as the development of what Shakespeare termed "Crabbed Age," with its associated mental inflexibility and inflexibility and sometimes bitterness of personality.

Shakespeare and the literature of old age remind us that there is a wider set of changes that, whether linked to vascular processes or not, have been eclipsed in the development of our currently prevailing models of dementia. There are likely to be syndromes other than age-associated memory impairment that deserve our attention. Our current models are in fact recent, hav-

ing originated only in the period 1975 through 2000. We may need to revert to a much broader concept like "lacunatic" if we are to recognize the full range of agents that might have functional effects upon aging.

A more enduring focus of attention has been on mild cognitive impairment, which led to the delineation of syndromes such as age-associated memory impairment and the benign senile forgetfulness first proposed by Kral in 1962. These states have been proposed as prodromes of more serious disease, the treatment of which might forestall the development of full-blown dementias. But would agents effective in states of mild cognitive impairment remain confined to a disease domain, or would they be employed as enhancement agents?

One of the great features of early twenty-first-century medicine has been a focus on enhancement. Agents first introduced for clear-cut organic disorders such as erectile dysfunction, as in the case of Viagra, have been adopted to enhance functioning in much younger populations without convincing evidence of an organic lesion. Similarly, drugs first developed for the narcoleptic syndrome, such as modafanil, have since been explored as agents to "optimize wakefulness."

It is almost certain that if agents showed beneficial effects on memory, there would be a much greater market in the domain of memory enhancement than in traditionally medical domains such as the treatment of dementia. Until the end of the twentieth century, such paramedical uses were constrained within a disease model, and the notion of enhancement would have brought a frown to the face of most physicians. However, by the start of the twenty-first century, medical reserve in these areas was diminishing, and there was far more open advocacy of enhancement models (Elliott 2003; Rothman and Rothman 2004). And it is worth noting that there is probably some middle ground between these medical and nonmedical domains in which it is possible to contemplate a maintenance of functionality in older age (Marshall and Katz 2002).

The question of cognitive enhancement probably has greater political resonance than the notion of enhancement in other domains. For instance, one of the bases on which discrimination is still permissible is intellectual ability. Children and others who perform better intellectually get to go to universities, and indeed are often subsidized to do so, and end up in better-paying jobs than children not so favored. "Smart" drugs, however, are more likely to help those less advantaged in the current educational system or those whose abilities have begun to fail by virtue of age. On this basis those currently most advantaged in society perhaps stand to lose most. Against this background, the

question of whether drugs should be widely available or constrained within a disease framework, albeit one that contains expanded concepts such as mild cognitive impairment, is a question with immense ramifications (Healy 2002; Rose 2002; Juengst et al. 2003).

It is highly likely that research on neurodegenerative disorders—for instance, research on glutamate—will lead to more effective agents to treat affective and schizophrenic disorders than will emerge from research programs dedicated to developing new antipsychotics or antidepressants. It is also likely that leads from drugs like haloperidol or orphenadrine that turn out to have unrecognized effects on glutamatergic or other systems will provide breakthroughs in the development of some agents that will enhance cognitive function and others that will arrest the pathological processes that underpin dementia. Should there be developments in either of these domains, our understanding of what the key lines of historical development in the field of psychopharmacology have been is likely to be transformed.

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