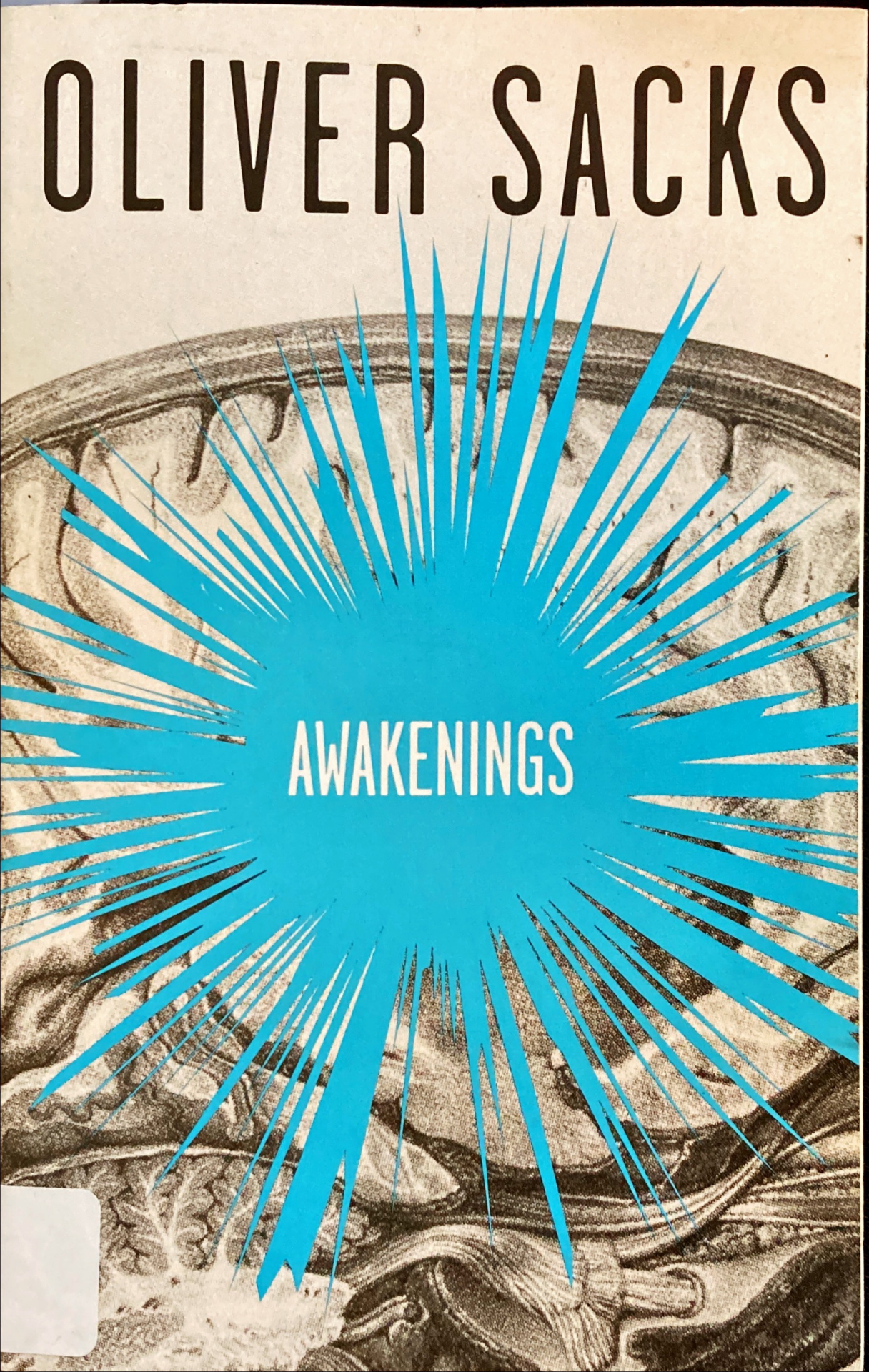
OLIVER SACKS



AWAKENINGS

FIRST VINTAGE BOOKS EDITION, SEPTEMBER 1999

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Library of Congress Cataloging-in-Publication Data
Sacks, Oliver W.
Awakenings / Oliver Sacks. — 1st Vintage Books ed.
p. cm.
Includes bibliographical references and index.
1. Postencephalitic Parkinson's disease Case studies. 2. Epidemic encephalitis—Complications Case studies. 3. Dopa—Therapeutic use Case studies. I. Title.
[RC382.S23 1999]
616.8'32—dc21 99-27880
CIP

Vintage Books Trade Paperback ISBN: 978-0-375-70405-5
eBook ISBN 978-0-307-83409-6

www.vintagebooks.com

Printed in the United States of America
23 22

The Sleeping-Sickness (Encephalitis Lethargica)[5]

In the winter of 1916–17, in Vienna and other cities, a "new" illness suddenly appeared, and rapidly spread, over the next three years, to become world-wide in its distribution. Its manifestations were so varied that no two patients ever presented exactly the same picture, and so strange as to call forth from physicians such diagnoses as epidemic delirium, epidemic schizophrenia, epidemic Parkinsonism, epidemic disseminated sclerosis, atypical rabies, atypical poliomyelitis, etc. etc. It seemed, at first, as if a thousand new diseases had suddenly broken loose, and it was only through the profound clinical acumen of Constantin von Economo, allied with his pathological studies on the brains of patients who had died, and his demonstration that these, beside showing a unique pattern of damage, contained a sub-microscopic, filter-passing agent (virus) which could transmit the disease to monkeys, that the identity of this protean disease was established. *Encephalitis lethargica*—as von Economo was to name it—was a Hydra with a thousand heads.

Although there had been innumerable smaller epidemics in the past, including the London sleeping-sickness of 1672–3[6]—there had never been a world-wide pandemic on the scale of that which started in 1916-17.[7] In the ten years that it raged, this

[5] The term "sleeping-sickness" is used in America to designate both the African, parasite-borne, endemic disease (*trypanosomiasis*) *and* the epidemic, virus-borne, *encephalitis lethargica*; in England, however, the latter is often called "sleepy-sickness."

[6] It is of historical (and perhaps epistemological) interest that Leibniz (whose ideas I shall often quote in this book) was himself in London at the time of the London sleeping-sickness, and there met Sydenham (who had described it under the name of "febris comatosa"), and the aged and then deeply-Parkinsonian Hobbes. The vast majority of Leibniz's 40,000-odd letters are still unsorted and unpublished; perhaps, one day, we will discover descriptions of Parkinsonism, and *encephalitis lethargica*, written by the hand of Leibniz himself.

[7] I have elsewhere (*B.M.J.*, 9 October 1971) detailed the 2000-year-long history of these epidemics: the following extract is taken from my B.M.J. letter: "The older literature is full of vivid accounts of feverish somnolent illnesses followed,

within months or years, by the development of characteristic slowness, poverty and difficulty of movement, masking, rigidity, tremors, and, on occasion, torticollis, dystonias, oculogyria, strabismus, blepharoclonus, myoclonus, catatonus, somnolence, etc., etc. The unique symptomology of such cases, so circumstantially described in the older literature, is scarcely compatible with any other illness *but* encephalitis lethargica with Parkinsonian and other typical sequelae. Many such accounts are collected and critically scrutinized in the encylopaedic works of von Economo and Jelliffe. Von Economo, while allowing that such retrospective diagnoses can only be tentative, concludes: "We may assume with some degree of certainty that encephalitis lethargica had already appeared *repeatedly* before the Great War, both sporadically in the shape of isolated cases and in epidemics which again and again attracted notice for a short period on account of the . . . singular combinations of symptoms displayed" (*op. cit.* pp. 8–9).

A few of these former cases and epidemics may be recalled. In 1580, Europe was swept by a serious febrile and lethargic illness ("Morbus epidemicus per totam fere Europam *Schlafkrankheit dictus* . . .), which led to Parkinsonian and other neurological sequelae. A similar serious epidemic occurred in London between 1673 and 1675, and is described by Sydenham as "febris comatosa"; hiccough was a prominent symptom in this epidemic (as in the Vienna encephalitis of 1919). Albrecht of Hildesheim, in 1695, provided an elaborate account of oculogyric crises, Parkinsonian symptoms, diplopia, strabismus, etc. following an attack of somnolent brain-fever in a 20-year-old girl ("De febre lethargica in strabismo utriusque oculi desinente"). A severe epidemic of *Schlafkrankheit* occurred in Tübingen in 1712 and 1713, and was followed in many cases by persistent slowness of movement and lack of initiative ("aboulia"). Minor epidemics of "coma somnolentum" with Parkinsonian features occurred in France and Germany during the latter half of the eighteenth century, alternating with hyperkinetic epidemics of hiccough, myoclonus, chorea, and tics. Many isolated cases of *juvenile* Parkinsonism, variously associated with diplopia, oculogyria, tachypnoea, retropulsion, tics, and obsessional disorders were described by Charcot, and were almost certainly postencephalitic in origin. In Italy, following the great influenza epidemic of 1889–90, the notorious "nona" appeared—a devastatingly severe somnolent illness which was followed by the development of Parkinsonian and other sequelae in almost all of the few survivors.

A knowledge of such historical accounts, and of the peculiar comings and goings of encephalitis lethargica in previous centuries, is of more than academic importance. A graphic description of the "nona," given by his mother to the young von Economo, enabled him to recognize and characterize this illness when it re-appeared in its catastrophic form in 1917; this is movingly described in the preface of his book. Jelliffe, in his many writings at the time of the great encephalitis epidemic, asks again and again how it could happen that a disease which had obviously existed since the days of Hippocrates could be "discovered" only now, and how it was possible for an illness which had been described unmistakably innumerable times to be "forgotten" anew by each generation. Such forgettings are as dangerous as they are mysterious, for they give us an unwarranted sense of security. In 1927, with the virtual cessation of new cases of encephalitis lethargica, the medical profession heaved a huge sigh of relief, and did its best to forget the horrors of the previous decade. Von Economo warned against this, saying that the causative virus was not extinct, but only in a dormant or non-virulent phase, from which it would inevitably re-emerge as it had done innumerable times since the dawn of recorded history.

pandemic took or ravaged the lives of nearly five million people before it disappeared, as mysteriously and suddenly as it had arrived, in 1927. A third of those affected died in the acute stages of the sleeping-sickness, in states of coma so deep as to preclude arousal, or in states of sleeplessness so intense as to preclude sedation. Patients who suffered but survived an extremely severe somnolent/insomniac attack of this kind often failed to recover their original aliveness. They would be conscious and aware—yet not fully awake; they would sit motionless and speechless all day in their chairs, totally lacking energy, impetus, initiative, motive, appetite, affect or desire; they registered what went on about them with profound indifference.[8] They neither conveyed nor felt the feeling of life; they were as insubstantial as ghosts, and as passive as zombies: von Economo compared them to extinct volcanoes. Such patients, in neurological parlance, showed "negative" disorders of behaviour, i.e. no behaviour at all. They were ontologically dead, or suspended, or "asleep"—awaiting an awakening which came (for the tiny fraction who survived) fifty years later.

If these "negative" states or *absences* were more varied and severe than those seen in common Parkinson's disease, this was even truer of the innumerable "positive" disorders or pathological *presences* introduced by the sleeping-sickness: indeed, von Economo, in his great monograph, enumerated more than five hundred distinct forms or varieties of these.

Parkinsonian disorders, of one sort or another, were perhaps the commonest of these disorders, although their appearance was often delayed until many years after the acute epidemic. Post-encephalitic Parkinsonism, as opposed to ordinary or idiopathic Parkinsonism, tended to show less in the way of tremor and rigidity—indeed, these were sometimes completely absent—but much severer states of "explosive" and "obstructive" disorders, of akinesia and akathisia, push and resistance, hurry and

[8] his heart transfixed,
Comatose in her cave, cares little
What the senses say. . . .
W. H. AUDEN

impediment, etc., and also much severer states of the compliant-perseverative type of akinesia which Gowers had compared to catalepsy. Many patients, indeed, were swallowed up in states of Parkinsonian akinesia so profound as to turn them into living statues—totally motionless for hours, days, weeks, or years on end. The very much greater severity of these encephalitic and post-encephalitic states revealed that *all* aspects of being and behaviour—perceptions, thoughts, appetites, and feelings, no less than movements—could also be brought to a virtual standstill by an active, constraining Parkinsonian process.

Almost as common as these Parkinsonian disorders, and frequently co-existing with them, were *catatonic* disorders of every sort. It was the occurrence of these which originally gave rise to the notion of an "epidemic schizophrenia," for catatonia—until its appearance in the encephalitis epidemic—was thought to be part-and-parcel of the schizophrenic syndrome. The majority of patients who were rendered catatonic by the sleeping-sickness were *not* schizophrenic, and showed that catatonia might, so to speak, be approached by a direct physiological path, and was not always a defensive manoevre undertaken by schizophrenic patients at periods of unendurable stress and desperation.[9]

The general forms or "phases" of encephalitic catatonia were closely analogous to those of Parkinsonism, but were at a higher and more complex level, and were usually experienced as subjective states which had exactly the same form as the observable behavioural states. Thus some of these patients showed automatic compliance or "obedience," maintaining (indefinitely, and apparently without effort) any posture in which they were put or found themselves, or "echoing" words, phrases, thoughts, perceptions or actions in an unvarying circular way, once these had been suggested to them (palilalia, echolalia, echopraxia, etc.). Other patients showed disorders of a precisely antithetical kind ("command negativism," "block," etc.) immediately preventing or countermanding any suggested or intended action,

[9] Post-encephalitic patients, when they can speak—which in the severest cases was not rendered possible until half a century later, when they were given L-DOPA—are thus able to provide us with uniquely detailed and accurate descriptions of states of catatonic "entrancement," "fascination," "block," "negativism" etc., which schizophrenic patients, usually, are unable or unwilling to do, or which they will only describe in distorted, magical, "schizophrenic" terms.

speech or thought: in the severest cases, "block" of this type could cause a virtual obliteration of all behaviour and also of all mental processes (see the case of Rose R., for example). Such constrained catatonic patients—like constrained Parkinsonians—could suddenly burst out of their immobilized states into violent movements or frenzies: a great many of the tics seen at the time of the epidemic, and subsequently, showed themselves to be interchangeable with "tics of immobility" (or catatonia).

An immense variety of involuntary and compulsive movements were seen during the acute phase of the encephalitis, and for a few years thereafter; myoclonic jerks and spasms; states of mobile spasm (athetosis), dystonias and dystonic contortions (e.g. torticollis), with somewhat similar functional organizations to that of Parkinsonian rigidity; desultory, forceless movements dancing from one part of the body to another (chorea); and a wide spectrum of tics and compulsive movements at every functional level—yawning, coughing, sniffing, gasping, panting, breath-holding, staring, glancing, bellowing, yelling, cursing, etc.—which were enactions of sudden *urges*.

At the "highest" level the *encephalitis lethargica* presented itself as neurotic and psychotic disorders of every kind, and a great many patients affected in this way were originally considered to have "functional" obsessional and hysterical neuroses, until the development of other symptoms indicated the encephalitic aetiology of their complaints. It is of interest, in this connection, that "oculogyric crises" were considered to be purely "functional" and hysterical for several years after their first appearance.

Clearly-differentiated forms of affective compulsion were common in the immediate aftermath of the sleeping-sickness especially erotomanias, erethisms, and libidinal excitements, on the one hand, and tantrums, rages and destructive outbursts, on the other. These forms of behaviour were most clearly and undisguisedly manifest in children, who sometimes showed abrupt changes of character, and suddenly became impulsive, provocative, destructive, audacious, salacious and lewd, sometimes to a quite uncontrollable degree: such children were often labelled "juvenile psychopaths" or "moral aments." Sexual and destruc-

tive outbursts were rarely outspoken in adults, being "converted" (presumably) to other, more "allowable," reactions and expressions. Jelliffe, in particular, who undertook lengthy analysis of some highly-intelligent post-encephalitic patients, showed unequivocally how accesses of erotic and hostile feeling could be and were "converted," not only into neurotic and psychotic behaviour, but into ties, "crises," catatonia and even Parkinsonism. Adult post-encephalitic patients thus showed an extraordinary ability to "absorb" intense feeling, and to express it in indirect physiological terms. They were gifted—or cursed—with a pathologically extravagant expressive facility or (in Freud's term) "somatic compliance."

Nearly half the survivors became liable to extraordinary crises, in which they might experience, for example, the simultaneous and virtually instantaneous onset of Parkinsonism, catatonia, tics, obsessions, hallucinations, "block," increased suggestibility or negativism, and thirty or forty other problems; such crises would last a few minutes or hours, and then disappear as suddenly as they had come. They were highly individual, no two patients ever having exactly the same sort of crisis, and they expressed, in various ways, fundamental aspects of the character, personality, history, perception and fantasies of each patient. These crises could be greatly influenced, for better or worse, by suggestion, emotional problems or current circumstances. Crises of all sorts became rare after 1930, but I stress them and their characteristics because they show remarkable affinities to certain states induced by L-DOPA, not merely in post-encephalitic patients, but in the normally much stabler patients with common Parkinson's disease.

One thing, and one alone, was (usually) spared amid the ravages of this otherwise engulfing disease: the "higher faculties"—intelligence, imagination, judgment, and humour. These were exempted—for better or worse. Thus these patients, some of whom had been thrust into the remotest or strangest extremities of human possibility, experienced their states with unsparing perspicacity, and retained the power to remember, to compare, to dissect, and to testify. Their fate, so to speak, was to become unique witnesses to a unique catastrophe.

The Aftermath of the Sleeping-Sickness (1927–1967)

Although many patients seemed to make a complete recovery from the sleeping-sickness, and were able to return to their former lives, the majority of them subsequently developed neurological or psychiatric disorders, and, most commonly, Parkinsonism. Why they should have developed such "post-encephalitic syndromes"—after years or decades of seemingly-perfect health—is a mystery, and has never been satisfactorily explained.

These post-encephalitic syndromes were very variable in course: sometimes they proceeded rapidly, leading to profound disability or death; sometimes very slowly; sometimes they progressed to a certain point and then stayed at this point for years or decades; and sometimes, following their initial onslaught, they remitted and disappeared. This great variation of pattern is also a mystery, and seems to admit of no single or simple explanation.

Certainly it could not be explained in terms of microscopically-visible disease-processes, as was considered at one time. Nor was it true to say that post-encephalitic patients were suffering from a "chronic encephalitis," for they showed no signs of active infection or inflammatory reaction. There was, moreover, a rather poor correlation between the severity of the clinical picture and that of the pathological picture, insofar as the latter could be judged by microscopic or chemical means: one saw profoundly-disabled patients with remarkably few signs of disease in the brain, and one saw evidences of widespread tissue-destruction in patients who were scarcely disabled at all. What *was* clear, from these discrepancies, was that there were many other determinants of clinical state and behaviour beside localized changes in the brain; it was clear that the susceptibility or propensity to Parkinsonism, for example, was not a fixed expression of lesions in the "Parkinsonism-centre" of the brain, but dependent on innumerable other "factors" in addition.

It seemed, as Jelliffe[10] and a few others repeatedly stressed, as if the "*quality*" of the individual—his "strengths" and "weaknesses," resistances and pliancies, motives and experiences, etc.—played a large part in determining the severity, course and form of his illness. Thus, in the 1930s, at a time of almost exclusive emphasis on specific mechanisms in physiology and pathology, the strange evolutions of illness in these post-encephalitic patients recalled Claude Bernard's concepts of the *terrain* and the *milieu interne*, and the immemorial ideas of "constitution," "diathesis," "idiosyncrasy," "predisposition," etc., which had become so unfashionable in the twentieth century. Equally clear, and beautifully analysed by Jelliffe, were the effects of the external environment, the circumstances and vicissitudes of each patient's life. Thus, post-encephalitic illness could by no means be considered a simple disease, but needed to be seen as an individual creation of the greatest complexity, determined not simply by a primary disease-process, but by a vast host of personal traits and social circumstances: an illness, in short, like neurosis or psychosis, a coming-to-terms of the sensitized individual with his total environment.[11] Such considerations, of course, are of crucial importance in understanding the total reactions of such patients to L-DOPA.

There remain today a few survivors of the encephalitis who, despite Parkinsonism, tics, or other problems, still lead active and independent lives (see for instance the case of Cecil M.). These are the fortunate minority, who for one reason or another have managed to keep afloat, and have not been engulfed by illness, disability, dependence, demoralization, etc.—Parkinson's "train of harassing evils."

But for the majority of post-encephalitic patients—in consequence of the basic severity of their illness, their "weaknesses," their propensities, or their misfortunes—a much darker future was in store. We have already stressed the inseparability of a patient's illness, his self, and his world, and how any or all of these, in their manifold interactions, through an infinity of vicious circles, can bring him to his nadir of being. How much is contributed by this, and that, and that, and that, can per-

[10] See p. 193 n.
[11] See notes on pp. 17 and 18.

haps be unravelled by the most prolongued, intimate contact with individual patients, but cannot be put in any general, universally-applicable form. One can only say that most of the survivors went down and down, through circle after circle of deepening illness, hopelessness and unimaginable solitude, their solitude, perhaps, the least bearable of all.

> As *Sicknes* is the greatest misery, so the greatest misery of sicknes, is *solitude* . . . *Solitude* is a torment which is not threatened in *hell* itselfe.
>
> Donne

The character of their illness changed. The early days of the epidemic had been a time of ebullition or ebullience, pathologically speaking, full of movements and tics, impulsions and impetuosities, manias and crises, ardencies and appetencies. By the late twenties, the acute phase was over, and the encephalitic syndromes started to cool or congeal. States of immobility and arrest had been distinctly uncommon in the early 1920s, but from 1930 onwards started to roll in a great sluggish, torpid tide over many of the survivors, enveloping them in metaphorical (if not physiological) equivalents of sleep or death. Parkinsonism, catatonia, melancholia, trance, passivity, immobility, frigidity, apathy: this was the quality of the decades-long "sleep" which closed over their heads in the 1930s and thereafter. Some patients, indeed, passed into a timeless state, an eventless stasis, which deprived them of all sense of history and happening. Isolated circumstances—fire-alarms, dinner-gongs, the unexpected arrival of friends or news—might set them suddenly and startlingly alive for a minute, wonderfully active and agog with excitement. But these were rare flashes in the depths of their darkness. For the most part, they lay motionless and speechless, and in some cases almost will-less and thoughtless, or with their thoughts and feelings unchangingly fixed at the point where the long "sleep" had closed in upon them. Their minds remained perfectly clear and unclouded, but their whole beings, so to speak, were encysted or cocooned.

Unable to work or to see to their needs, difficult to look after, helpless, hopeless, so bound up in their illnesses that they could

neither react nor relate, frequently abandoned by their friends and their families, without specific treatment of any use to them—these patients were put away in chronic hospitals, nursing homes, lunatic asylums, or special colonies; and there, for the most part, they were totally forgotten—the lepers of the present century; there they died in their hundreds of thousands.

And yet some lived on, in diminishing numbers, getting older and frailer (though usually looking younger than their age), inmates of institutions, profoundly isolated, deprived of experience, half-forgetting, half-dreaming of the world they once lived in.

Life at Mount Carmel

Mount Carmel was opened, shortly after the First World War, for war-veterans with injuries of the nervous system, and for the expected victims of the sleeping-sickness. It was a cottage-hospital, in these early days, with no more than forty beds, large grounds, and a pleasant prospect of surrounding countryside. It lay close to the village of Bexley-on-Hudson, and there was a free and friendly exchange between the hospital and the village: patients often went to the village for shopping, or meals, or silent movies, and the villagers, in turn, frequently visited the hospital; there were dates, and dances, and occasional marriages; and there were friendly rivalries in bowls and football, in which the measured deliberation of the villagers would be met by the abnormal suddenness and speed of movement characteristic of so many encephalitic patients, fifty years ago.

All this has changed, with the passage of years. Bexley-on-Hudson is no longer a village, but a crowded and squalid suburb of New York; the leisurely life of the village has gone, to be replaced by the hectic and harried anti-life of New York; Bexleyites no longer have any time, and rarely spare a thought for the hospital among them; and Mount Carmel itself has grown sick from hypertrophy, for it is now a 1000-bed Institution

which has swallowed its grounds; its windows no longer open on pleasant gardens or country, but on ant-nest suburbia, or nothing at all.

Still sadder, and more serious, has been the change in its character, the insidious deterioration in "atmosphere" and *care*. In its earlier days—indeed, before 1960—the hospital was both easy-going and secure; there were devoted nurses and others who had been there for years, and most of the medical positions were honorary and voluntary, calling forth the best side, the kindness, of visiting doctors; and though its patients had grown older and frailer, they could look forward to excursions, day-trips, and summer-camps. In the past ten years, and especially the last three years, almost all this has changed. The hospital has assumed somewhat the aspect of a fortress or prison, in its physical appearance and the way it is run. A strict Administration has come into being, rigidly committed to "efficiency" and rules; "familiarity" with patients is strongly discouraged. Law and order have been ousting fellow-feeling and kinship; hierarchy separates the inmates from staff; and patients tend to feel they are "inside," unreachably distant from the real world outside. There are, of course, gaps in this totalitarian structure, where *real* care and affection still maintain a foothold: many of the "lower" staff—nurses, aides, orderlies, physiotherapists, occupational therapists, speech therapists, etc.—give themselves unstintingly, and with love, to the patients; volunteers from the neighbourhood provide non-professional care; and, of course, *some* patients are visited by relatives and friends. The hospital, in short, is a singular mixture, where freedom and bondage, warmth and coldness, human and mechanical, life and death, are locked together in perpetual combat.[12]

In 1966, when I first went to Mount Carmel, there were still

[12] We have seen that Parkinsonism and neurosis are innately coercive, and share a similar *coercive structure*. Rigorous institutions are also coercive, being, in effect, *external neuroses*. The coercions of institutions call forth and aggravate the coercions of their inmates: thus one may observe, with exemplary clarity, how the coerciveness of Mount Carmel aggravated neurotic and Parkinsonian tendencies in post-encephalitic patients; one may also observe, with equal clarity, how the "good" aspects of Mount Carmel—its sympathy and humanity—reduced neurotic and Parkinsonian symptoms. Hobbes, in the extended metaphor of *Leviathan*, explores the analogies of the Body and the State, seeing sickness in both as constitution-by-force.

some eighty post-encephalitic patients there, the largest, and perhaps the only, such group remaining in the United States, and one of the very few such groups remaining in the world. Almost half of these patients were immersed in states of pathological "sleep," virtually speechless and motionless, and requiring total nursing-care; the remainder were less disabled, less dependent, less isolated and less depressed, could look after many of their own basic needs, and maintain a modicum of personal and social life. Sexuality, of course, was *forbidden* in Mount Carmel.

Between 1966 and 1969, we brought the majority of our post-encephalitic patients (many of whom had been immured in remote, unnoticed bays of the hospital) into a single, organic, and self-governing community; we did what we could to give them the sense of being *people*, and not condemned prisoners in a vast Institution; we instituted a search for missing relatives and friends, hoping that *some* relationships—broken by time and indolence, rather than hostility and guilt—might thus be reforged; and I myself formed with them such relationships as I could.

These years, then, saw a certain establishment of sympathies and kinships, and a certain melting-away of the rigid staff/inmate dichotomy; and with these, and all other forms of treatment, a certain—but pitifully limited—improvement in their overall condition, neurological and otherwise. Opposing all forms of therapeutic endeavour, and setting a low ceiling on what could be achieved, was the crushing weight of their illness, the Saturnian gravity of their Parkinsonism, etc.; and behind this, and mingling with it, all the dilapidations, impoverishments, and perversions of long isolation and immurement.[13]

[13] It is of the greatest interest to compare the state of these patients at Mount Carmel with that of the only-existing post-encephalitic community in England (at the Highlands Hospital). Conditions at Highlands—where there are large grounds, free access to and from a neighbouring community, devoted attention, and a much freer and easier atmosphere—are akin to those which obtained at Mount Carmel in its early days. The patients at Highlands (most of whom have been there since the 1920s) although they have severe post-encephalitic syndromes, convey an altogether different appearance from the patients at Mount Carmel. They tend, by and large, to be mercurial, sprightly, impetuous and hyper-active—with vivid and ardent emotional reactions. This is in the greatest contrast to the

Some of these patients had achieved a state of icy hopelessness akin to serenity: a realistic hopelessness, in those pre-DOPA days; they *knew* they were doomed, and they accepted this with all the courage and equanimity they could muster. Other patients (and, perhaps, to some extent, all of these patients, whatever their surface serenity) had a fierce and impotent sense of outrage: they had been *swindled* out of the best years of life; they were consumed by the sense of time lost, time *wasted*; and they yearned incessantly for a twofold miracle—not only a cure for their sickness, but an indemnification for the loss of their lives. They wanted to be given back the time they had lost, to be magically replaced in their youth and their prime.

These were their expectations before the coming of L-DOPA.

The Coming of L-DOPA

L-DOPA is a "miracle-drug"—the term is used everywhere; and this, perhaps, is scarcely surprising, for the physician who pioneered its use—Dr. Cotzias—himself calls L-DOPA "a true miracle-drug . . . of our age." It is curious to hear sober physicians, and others, in the twentieth century, speaking of "miracles," and describing a drug in millennial terms. And the fervid enthusiasm aroused by reports of L-DOPA, both in the world at large and among physicians who give it and patients who take it—this too is amazing, and suggests that feelings and phantasies of an extraordinary nature are being excited and indulged. The L-DOPA "story" has been intimately interwoven, for the last six years, with fervours and feelings of a mystical type; it cannot

deeply Parkinsonian, entranced, grave or withdrawn appearance of so many patients at Mount Carmel. It is clear that both groups of patient have the same disease, and it is equally clear that the *form* and evolution of illness have been quite different in the two groups. My visits to Highlands have always given me the strangest double sense of mixed familiarity and unfamiliarity, as I saw a large group of patients so similar, yet so dissimilar, to ours at Mount Carmel. Nothing has brought home to me so clearly the overwhelming effect which life-style and life circumstances may have on the development of post-encephalitic illness.

be understood without reference to these; and it would be quite misleading to present it in purely literal and historical terms.

We rationalize, we dissimulate, we pretend: we pretend that Modern Medicine is a Rational Science, all facts, no nonsense, and just what it seems. But we have only to tap its glossy veneer for it to split wide-open, and reveal to us its roots and foundations, its old dark heart of metaphysics, mysticism, magic, and myth. Medicine is the oldest of the arts, and the oldest of the sciences: would one not expect it to spring from the deepest knowledge and feelings we have?

There is, of course, an ordinary medicine, an everyday medicine, humdrum, prosaic, a medicine for stubbed toes, quinsies, bunions, and boils; but all of us entertain the idea of *another* sort of medicine, of a wholly different kind: something deeper, older, extraordinary, almost sacred, which will restore to us our lost health and wholeness, and give us a sense of perfect well-being.

For all of us have a basic, intuitive feeling that once we *were* whole and well; at ease, at peace, at home in the world; totally united with the grounds of our being; and that then we lost this primal, happy, innocent state, and fell into our present sickness and suffering. We had something of infinite beauty and preciousness—and we lost it; we spend our lives searching for what we have lost; and one day, perhaps, we will suddenly find it. And this will be the miracle, the millennium!

We may expect to find such ideas most intense in those who are enduring extremities of suffering, sickness, and anguish, in those who are consumed by the sense of what they have lost, or wasted, and by the urgency of recouping before it is too late. Such people, or patients, come to priests or physicians in desperations of yearning, prepared to believe anything for a reprieve, a rescue, a regeneration, a redemption. They are credulous in proportion to their desperation—the predestined victims of quacks and enthusiasts.

This sense of what is lost, and what must be found, is essentially a metaphysical one. If we arrest the patient in his metaphysical search, and ask him *what it is* that he wishes or seeks, he will not give us a tabulated list of items, but will say,

simply, "My happiness," "My lost health," "My former condition," "A sense of reality," "Feeling fully alive," etc. He does not long for this thing or that; he longs for a *general* change in the complexion of things, for everything to be *alright* once again, unblemished, the way it once was. And it is at this point, when he is searching, here and there, with so painful an urgency, that he may be led into a sudden, grotesque mistake; that he may (in Donne's words) mistake "the Apothecaryes shop" for "the Metaphoricall Deity": a mistake which the apothecary or physician may be tempted to encourage.

It is at this point that he, ingenuously, and his apothecary and doctor, perhaps disingenuously, together depart from reality, and that the basic metaphysical truth is suddenly twisted, (and replaced by a fantastic, mechanical corruption or falsehood). The chimerical concept which now takes its place is one of the delusions of vitalism or materialism, the notion that "health," "well-being," "happiness," etc. can be reduced to certain "factors" or "elements"—principles, fluids, humours, commodities—*things* which can be measured and weighed, bought and sold. Health, thus conceived, is reduced to a *level*, something to be titrated or topped-up in a mechanical way. Metaphysics in itself makes no such reductions: its terms are those of organization or design. The fraudulent reduction comes from alchemists, witch-doctors, and their modern equivalents, and from patients who long *at all costs* to be well.

It is from this debased metaphysics that there arises the notion of a mystical substance, a miraculous drug, something which will assuage all our hungers and ills, and deliver us instantly from our miserable state: metaphorical equivalents of the Elixir of Life.[14] Such notions and hopes fully retain today their ancient,

[14] The notion of "mystical substances" arises from a *reductio ad absurdum* of two world-views which, legitimately employed, have great elegance and power: one is the mosaic or topist view, associated with the philosophies of empiricism and positivism, and the other is a holist or monist view. These derive, respectively, from Aristotelian and Platonic metaphysics. Used with mastery, and a full understanding of their powers and limits, these two world-views have provided a groundwork for fundamental discoveries in physiology and psychology during the past two hundred years.

Mysticism arises by taking analogy for identity—turning similes and metaphors (or "as" statements) into absolutes (or "is" statements), converting a useful epistemology into "absolute truth." A mystical topism asserts that the world

magical, mythical force, and—however we may disavow them—show themselves in the very words we use: "vitamins" (vital amines), and the vitamin-cult; or "biogenic amines" (life-giving amines)—of which dopamine (the biologically-active substance into which L-DOPA is converted) is itself an example.

The notion of such mystical, life-giving, sacramental remedies gives rise to innumerable cults and fads, and to enthusiasms of a particularly extravagant and intransigeant type. One sees this in Freud's espousal of the drug cocaine[15]; in the first wild reactions to the appearance of cortisone, when some medical conferences, in the words of a contemporary observer, "more closely resembled revivalist meetings"; in the present world-wide "drug-

consists of a multitude of points, places, particles or pieces, without intrinsic relation to each other, but "extrinsically" related by a "causal nexus": it asserts this both exclusively and conclusively—it is "the truth," "the whole truth," and excludes any other "truth." Given such a view, one can conceive the possibility of affecting a single point or particle, without the least effect on those surrounding it: one would, for example, be able to *knock out* one point with absolute accuracy and specificity. The therapeutic correlate of such a mysticism is the notion of *a perfect Specific*, which has exactly the effect one wants, and no possibility of any other effects. A famous example of such a supposed Specific is the drug arsphenamine, devised by Ehrlich for the treatment of syphilis. Ehrlich's own modest and realistic claims were immediately distorted by absolutist wishes and tendencies—and arsephenamine was soon dubbed "The Magic Bullet." *This* sort of mystical medicine, then, is dedicated to the search for more and more "magic bullets."

A mystical holism, conversely, asserts that the world is an entirely uniform and undifferentiated mass of "world-stuff," "primal matter," or plasm. A famous example of such a mystical-holist physiology is exemplified by a dictum ascribed to Flourens: "The brain is homogeneous like the liver; the brain secretes thought as the liver secretes bile." The therapeutic correlate of such a monist mysticism is the notion of an all-purpose drug, a Panacea or Catholicon, a Quintessential extract of World-Stuff or Brain-Stuff, absolutely pure bottled Goodness or Godness (or Guinness)—de Quincey's "portable ecstasy corked up in a pink-bottle" (*Confessions*, Everyman edition, p. 179).

It should be added that both of these mystical reductions finally boil down to the same thing (nothing), and this is scarcely surprising because they form opposite faces of a two-faced mistake. There is an essential difference between the legitimate, epistemological form of Topism and Holism, and their illegitimate, mystical forms. In the former there is a clear knowledge and acknowledgement of the *episteme* itself—the mode of knowledge, the grounds of conception, and how these lie with respect to the world. The mystical forms resemble delusions or *agnosias*, with overlooking of what they overlook, and denial that they deny: they represent incurable forms of epistemological disease. Such deteriorated epistemologies—as Wittgenstein noted—are like ladders with rotten rungs; one tries to climb up to "Truth" with their aid, but the ladder continually gives way beneath one.

[15] See Appendix.

scene"[16]; and, not least, in our present enthusiasm for the drug L-DOPA. It is impossible to avoid the feeling that here, over and above all legitimate enthusiasms, there is this special enthusiasm, this mysticism, of a magical sort.[17]

We may now pass on to the "straight" story of L-DOPA, remembering the mystical thread which always winds through it. Parkinson himself looked in vain for the "seat" or substrate of Parkinsonism, although he tentatively located it in the "pith" of the lower or medullary parts of the brain. Nor was there any real success in defining the location and nature of the pathological process until a century after the publication of Parkinson's "Essay."[18] In 1917 von Economo described the finding of severe damage to the *substantia nigra* (a nucleus in the midbrain, consisting of large pigmented cells) in a number of patients with *encephalitis lethargica* who had shown severe Parkinsonian symptoms. The following year Greenfield, in England, and pathologists elsewhere, were able to define similar, but milder,

[16] William James (*Varieties*, pp. 304–8; see Appendix) suggests that one of the primary reasons why people turn to alcohol is to achieve a sense of mystic at-oneness, a return to elemental and primal bliss, and that in this partly-metaphysical and partly-regressive use it exemplifies the deeply-felt need for "mystagogue" drugs; he quotes with approval the familiar maxim that "the best cure for dipsomania is religiomania."

We see from history and anthropology that the craving for mystagogues is universal and ancient, and that a wide knowledge of mystagogues is possessed by all races. The use of mystagogues, in the last century, constituted a literary pastime (and at times a necessity), and was part-and-parcel of the development of the Romantic Imagination. In our own century, especially in the last twenty years, the use of mystagogues has again become widespread and explicit, Huxley taking mescal to "cleanse the doors of perception," and Leary promoting LSD as a "sacramental" drug. Here—as with L-DOPA—one sees the amalgamation of genuine needs with mystical means, the mistaking of an infinite, metaphorical symbol for a finite, ingestible drug.

[17] An entertaining, instructive yet pernicious example of this came to my attention when a medical letter of mine ("Incontinent nostalgia due to L-DOPA," *Lancet*, 27 June 1970, p. 1394) was released to the Press, and appeared in more and more garbled and extravagant versions: one paper put into my mouth the amazing claim that I could revive the dead by the use of L-DOPA.

[18] There had, in fact, been tentative earlier localizations of a prescient sort, e.g. a famous case, in the 1890s, in which the development of a one-sided Parkinsonism was correlated with the growth of a tuberculoma of one cerebral peduncle; several cases of syphilitic disease of the midbrain, associated with Parkinsonism, etc. The organization of Parkinsonism, indeed, was appreciated, both theoretically and practically, *before* the finding of specific cell-damage: thus two operations for Parkinsonism—cutting the posterior spinal roots, and excising portions of the cerebral cortex—were performed, and found useful, before 1910.

changes in these cells in patients who had had ordinary Parkinson's disease. These findings, in company with other pathological and physiological work, suggested the existence of a clearly-defined *system*, linking the *substantia nigra* to other parts of the brain: a system whose malfunctioning or destruction might give rise to Parkinsonian symptoms. In Greenfield's words:

> . . . A general survey has shown *paralysis agitans* in its classical form to be a systemic degeneration of a special type affecting a neuronal system whose nodal point is the *substantia nigra*.

In 1920 the Vogts, with remarkable insight, suggested that this anatomically- and functionally-distinct system, might correspond with a *chemically-distinct* system, and that a specific treatment for Parkinsonism, and related disorders, might become possible if this hypothetical chemical substrate could be identified and administered.

> Studies should answer the question [they wrote], whether the striatal system or parts of it do or do not possess a special disposition towards certain injuring agents . . . Such a positive or negative tendency to react can be assumed to be ultimately due to the specific chemistry of the corresponding centre. The disclosure of the existence of such specific chemistry represents, in turn, at least the first step towards elucidation of its true nature, thereby initiating the development of a biochemical approach to treatment . . .

Thus, in the 1920s, there was not merely a vague notion of "something missing" in Parkinsonian patients (such as Charcot had entertained), but a clear path of research stretching out, pointing towards a prospect of ultimate success.

The most astute clinical neurologists, however, had reservations about this: was there not *structural* damage in the *substantia nigra*, and perhaps elsewhere, damage to nerve-cells and their connections? Could *this* be reversed? Would the administration of the missing chemical substrate be sufficient, or safe, given a marked degree of structural disorganization? Might there not be some danger of over-stimulating or over-loading such cells as were left? These reservations were expressed, with great pungency, by Kinniar Wilson:

> *Paralysis agitans* seems at present an incurable malady *par excellence*; the antidote to the "local death" of cell-fibre systems would be the equally elusive "elixir of life" . . . It is worse than useless to administer to the Parkinsonian any kind of nerve tonic to "whip up" his decaying cells; rather must some form of readily assimilable pabulum be sought, in the hope of supplying from without what the cell itself cannot obtain from within.

Neurochemistry, as a science, scarcely existed in the 1920s, and the project envisaged by the Vogts had to await its slow development. The intermediate stages of this research form a fascinating story in themselves, but will be omitted from consideration here. Suffice it that in 1960 Hornykiewicz, in Vienna, and Barbeau, in Montreal, using different approaches, but almost simultaneously, provided clear evidence that the affected parts of the brain in Parkinsonian patients were defective in the nerve-transmitter *dopamine*, and that the transfer and metabolism of dopamine in these areas was also disturbed. Immediate efforts were made to replenish the brain-dopamine in Parkinsonian patients by giving them the natural precursor of dopamine—Laevodihydroxyphenylalanine, or L-DOPA (dopamine itself could not pass into the brain). The results of these early therapeutic efforts were encouraging but inconclusive, and seven more years of arduous research had to be undertaken. Early in 1967, Dr. Cotzias and his colleagues, in their now-classic paper, were able to report a resounding therapeutic success in the treatment of Parkinsonism, giving massive doses of L-DOPA by mouth.[19]

The impact of Dr. Cotzias' work was immediate and astounding in the neurological world. The good news spread quickly. By March 1967, the post-encephalitic and Parkinsonian patients at Mount Carmel had already heard of L-DOPA: *some* of them were eager to try it at once; some had reservations and doubts, and wished to see its effects on others before they tried it themselves; some expressed total indifference; and some of course were unable to signal any reaction.

The cost of L-DOPA in 1967 and 1968 was exceedingly high

[19] Dr. Cotzias' first work used DL-DOPA, a mixture of the biologically-active L-DOPA with its inactive isomer D-DOPA. The separation of these two isomers, in 1966–7, was not easily accomplished, and was exceedingly costly.

(more than £2000 a pound), and it was impossible for Mount Carmel—a charity hospital, impoverished, unknown, unattached to any university or foundation, beneath the notice of drug-firms, industrial, or government sponsors—to buy L-DOPA at this time. Towards the end of 1968, the cost of L-DOPA started a sharp decline, and in March 1969 it was first used at Mount Carmel. The cases that follow are a sample of the stories of more than 200 patients to whom I administered L-DOPA during the next three years.

Library of Congress Cataloging in Publication Data

Sacks, Oliver W.
Awakenings.

1. Sleeping-sickness—Cases, clinical reports, statistics. 2. Paralysis agitans. I. Title.
[DNLM: 1. Dopa—Therapeutic use. 2. Encephalitis, Epidemic—Drug therapy. 3. Parkinsonism—Drug therapy. QV129 S121a 1974]
RC186.T82S3 1974 616.8'32
ISBN: 0-385-03562-4
Library of Congress Catalog Card Number 73-15363

Printed in the United States of America
First Edition in the United States