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 George Cotzias – himself calls L-DOPA 'a true miracle-drug . . . of our age.'[30] 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 be understood without reference to these; and it would be quite misleading to present it in purely literal and historical terms.

We rationalize, we dissimilate, 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,

[30] One of the great surprises (or should one say providences?) of nature is that the plant world contains so many substances which have a profound effect upon animals – and yet, apparently, are of no obvious 'use' to the plant. Thus the foxglove *(Digitalis)* contains digitalis glycosides, which are invaluable in the treatment of heart-failure; the autumn crocus *(Colchicum)* contains colchicine, invaluable in the treatment of gout, etc., etc. It is again characteristic that many such 'natural remedies' are discovered at a very early stage of human history, and may form part-and-parcel of a folk-medicine long before their efficacy is allowed by conventional or established medical science. It has recently been established, by chemical analysis, that several species of bean (especially the fava bean) contain large amounts of L-DOPA (of the order of 25 gm. L-DOPA in a pound of beans). There is also a suggestion (which requires careful examination) that such L-DOPA-rich beans may have constituted a 'folk-remedy' for Parkinsonians for many centuries, if not longer. Thus although we ascribe 'The Coming of L-DOPA' to A.D. 1967, it may well have 'come' by 1967 B.C.

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 *all right* 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) mis-

take '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.[31]

[31] 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 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 arsephenamine, 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 – de Quincey's 'portable ecstasy corked up in a pink-bottle.'

Such notions and hopes fully retain today their ancient, 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 intransigent type. One sees this in Freud's espousal of the drug cocaine;[32] 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-scene';[33] and, not least, in our present enthusiasm for the drug

[32] See Appendix: 'Miracle' Drugs: Freud, William James, and Havelock Ellis, p. 323.

[33] William James (*Varieties,* pp. 304–8) 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

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.

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.'[34] In 1919 von Economo, and separately Trétiakoff, described the findings 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, 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

genuine needs with mystical means, the mistaking of an infinite, metaphorical symbol for a finite, ingestible drug.

[34] 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.

Parkinsonism, and related disorders, might become possible if this hypothetical chemical substance 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 Parkinsonism 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 Kinnier 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).[35] 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.[36]

The impact of Cotzias's 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

[35] In contrast, the drug amantadine (introduced as an antiviral agent against influenza A, but discovered serendipitously in 1968 to have anti-Parkinsonian effects as well) acts either by inhibiting dopamine re-uptake, or by increasing its release, or both, effectively increasing the brain's own dopamine. More recently a variety of dopamine agonists (e.g., bromocriptine and pergolide) have been made, which also potentiate dopamine action in the brain; it is hoped that they may have more specific effects than L-DOPA, because their action may be confined to specific receptor sites.

In the past two or three years there have been intriguing trials of tissue transplants – transplanting foetal brain cells, or adult adrenal cells, directly into the brain, where (hopefully) they may survive as living 'dopamine pumps' (see Appendix: Beyond L-DOPA, p. 333).

[36] Cotzias's 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 $5,000 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.

I could, perhaps, despite its cost, have started a few of our patients on L-DOPA after reading Cotzias's paper. But I hesitated – and hesitated for two years. For the patients under my care were not 'ordinary' patients with Parkinson's disease: they had far more complex pathophysiological syndromes, and their situations were more complex, indeed without precedent – for they had been institutionalised, and out of the world, for decades – in some cases since the time of the great epidemic. Thus even before I started, I was faced by scientific and human complexities, complexities and perplexities of a sort which had not arisen in previous trials of levodopa, or indeed of any treatment in the past. Thus there was an element of the extraordinary, the unprecedented, the unpredictable. I was setting out, with my patients, on an uncharted sea . . .

I did not know what might happen, what might be released – the more so as some of my patients had been violently impulsive and hyperkinetic *before* being enclosed in a straightjacket of Parkinsonism. But as illness and death claimed some of my patients – especially in the fierce summer of 1968 – the need to do something became ever clearer and stronger, finally moving me to start L-DOPA, though with great caution, in March 1969.