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Parkinsonism: Neurological Considerations

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PARKINSONISM: NEUROLOGICAL CONSIDERATIONS

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In this discussion we shall concern ourselves with: 1. a brief review of current theories on the genesis and maintenance of alternating tremor and rigidity; 2. the clinical features of Parkinsonism with attention to *early* symptoms and signs; and 3. the medical treatment, including some comments of clinical interest on the chemistry and pharmacology of anti-Parkinson drugs. Modern surgical methods of treatment (chemopallidolysis, etc.) will not be considered in this paper.

A. The Pathophysiology of Parkinsonism

Whatever the type of Parkinsonism (v. i.), the hallmark of the syndrome is rest tremor and/or rigidity; in fact, some have contended that this pervading rigidity is the basis of almost all other disorders of movement in Parkinsonism—to wit, the abnormalities of gait and posture, the diminished rate and frequency of movement, etc. Now, the exact neural mechanism responsible for the origin and persistence of this rigidity and tremor remains one of the major mysteries of this syndrome. In other words, we still think of Parkinsonism as a classic example of so-called basal ganglia disease; and rightly so, in that the pathology, at least, is concentrated primarily in the substantia nigra and globus pallidus, less consistently in the striatum, and even less conspicuously in the red nucleus, all of which are definite constitutents of the basal ganglia. But, though we know *where* lesions are common, we do not know exactly *how* these particular lesions so disturb the normally smooth functioning of interdependent pyramidal and extrapyramidal systems as to produce alternating tremor and rigidity, the two cardinal symptoms and signs. Theories, evolved from the facts of pathologic anatomy and physiology in humans and in experimental animals, have generally pointed to the tremor and rigidity as 'release' phenomena, a loss of modulation, the result of a break in the "chain of (motor) command", as it were. Despite general acceptance of this 'release' concept, however, there are differences of opinion on exactly what is released. For example, Bucy interprets the globus pallidus lesions as a break in the "chain of command" from cortical suppressor area 4S to primary motor area 4—in other words, he bases his theory on the presumed normal regulatory influence of suppressor area 4S on motor area 4 by way of the suppressor circuit running from 4S to caudate nucleus, then to the globus pallidus, then to the thalamus (ventro-lateral nucleus), then back to area 4; thus when the globus pallidus link is damaged as in Parkinsonism, the suppressor circuit chain is broken, and tremor (and rigidity) result from the unsuppressed pyramidal outflow from area 4. On the other hand, Jenkner and Ward[7] and Falkerts and Spiegel[6] on the basis of experimental work on animals (both stimulation and destruction experiments on the reticular formation in the mid-brain tegmentum) feel that the globus pallidus (and substantia nigra) lesions release other normally subservient nuclear groups in the brain stem reticular formation from pallidal and nigral control, giving free rein to these other nuclear groups which give rise to the reticulo-spinal tract, the extrapyramidal system's major 'voice' in influencing lower motor neurone activity at all spinal levels. Thus, Bucy sees all this as a break in

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suppressor circuit influence on *pyramidal* outflow while other investigators see it as a break in pallidal and nigral control of downstream (reticulospinal) *extrapyramidal* outflow. In this setting of conflicting views and unproven theories, the basic pathophysiology is still to be explained.

The most recent ray of hope for better understanding of this tremor-rigidity problem is the work of Granit[8] who points out that not only the upper motor neurone (both pyramidal and extra pyramidal components) but also the lower motor neurone plays an important role in regulating muscle tone. This lower motor neurone mechanism, the so-called gamma loop, is a "feed-back" or "servo-system", originating in the small gamma anterior horn cells which innervate the muscle spindle fibers; innervated, these fibers contract and, by stretching the sense organ in the spindle, set up afferent stimuli to the large alpha anterior horn cells which innervate the started muscles and hence directly influence their tone and movement, disorders of which characterize Parkinsonism. Thus, from Granit's work it is clear that the alpha anterior horn cells can be driven indirectly through the gamma loop to the spindles as well as directly by other pathways covering upon the alphas. This all ties in, in theory at least, with the role of the central neural mechanisms described above in that the gamma system appears to be activated particularly by the brain stem reticular formation (extrapyramidal) and the alpha cells to be activated by the pyramidal tract. At this time, it is fair to say that this very recent addition to our knowledge of the control of movement is still too young to have borne definite clinical 'fruit'.

B. The Clinical Features of Parkinsonism

Whereas the inner workings of this syndrome remain an enigma, the outer trappings of the advanced stage, at least, are familiar to everyone. The combination of rest tremor, rigidity, poverty and inertia of movement, the loss of associated and expressional movements of arms and face; the masked facies and monotonous speech; the drooling; the shuffling or festinating gait—this is, unmistakably, advanced Parkinsonism. There is no problem in diagnosis here except in our attempt to categorize further as: idiopathic, post-encephalitic, or arteriosclerotic. Despite arguments to the contrary, in practice this can be difficult. With a history of encephalitis, of insidious onset of rigidity first and foremost, of oculo-gyric crises, of drowsiness, and of deficits in convergence and accommodation, a diagnosis of post-encephalitic type is justified; but, in my experience this is *not* a common happenstance. If, on the other hand, the patient is in the fifth or sixth decade and notices rather sudden onset of the characteristic tremor, followed by the other signs described previously, then a diagnosis of idiopathic type would be reasonable; this, by the way, is the type that Parkinson described in his 1817 Essay On The Shaking Palsy (or Paralysis Agitans). Finally, if the patient is in his seventh or eighth decade, is coincidentally hypertensive with mild to moderate dementia and possibly some pseudobulbar symptoms, and develops rigidity insidiously, then the arteriosclerotic type is probable.

The *early* Parkinsonism of insidious onset can be missed, especially in patients in the third to fifth decades, unless we pay particular attention to their complaints of stiffness or heaviness of the arms and legs, weakness or slowness, fatigability and muscle cramps or, even more obscurely, "deadness or numbness" of the arms and legs. In the

setting of these complaints, we must recognize the significance of our findings of reduced frequency of lid-blinking, failure of one or both arms to swing automatically when the patient walks, rigidity in the *proximal* joints (shoulder and hip), difficulty with the rapid rhythmic alternating movements of fingers and hands, the tendency for handwriting to get smaller and smaller the longer the patient writes at one sitting. There is also a so-called "spiked knuckles" sign, indicating the relative prominence of the metacarpophalangeal joints due to the dominance of finger flexor tendon tone over extensor tendon tone in early Parkinsonism. It is also important to recognize that unilateral involvement of the face, arm, and leg in these early cases is common and constitutes the so-called hemi-Parkinsonism. Even in these early cases, the slowness or inertia in the beginnings and endings of movements may be brought out and easily seen when the patient attempts a 90 degree or, particularly, a 180 degree turn while walking; in so doing, the rate of leg movement is conspicuously slowed and the rhythm disturbed until straight-line walking is again attained.

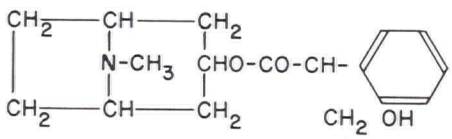
In the differential diagnosis, rarely an intracranial tumor, primary or metastatic, in the neighborhood of the basal ganglia may mimic the clinical picture described, particularly the hemi-Parkinsonism.

C. The Medical Treatment of Parkinsonism

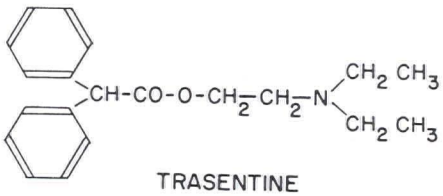
The total care of these patients has three major aspects—1. pharmaceutical; 2. physiotherapeutic; 3. psychiatric. For the most part those of us in office practice lean heavily on the first of these and take care of the second and third needs by urging and helping the patient to seek new channels of expression, at both physical and verbal levels, during every visit to our office. The special skills of physiatrist or psychiatrist may and should be sought when indicated, of course. Physiotherapy, for example, has something to offer in posture-correction, gait-training, muscle-stretching, progressive resistive exercises, and occupational therapy.

The treatment of Parkinsonism is symptomatic, of course, since the underlying neural mechanisms are still not understood. The major symptoms treated are, of course, tremor and rigidity with all their by-products.

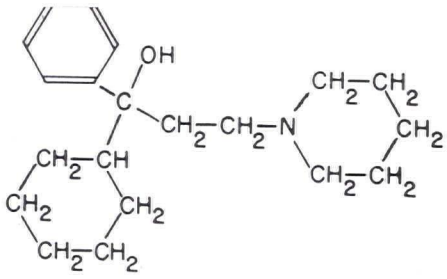
There is an already abundant but ever-increasing supply of pharmaceuticals of value in treating Parkinsonism, but they all come under the heading of four main drug groups—namely, *potato plant products and derivatives* (the solanaceous alkaloids); the *synthetic anti-spasmodics;* the *synthetic anti-histaminics;* the *synthetic cerebral stimulants*. The potato plant products which include Atropine, Hyoscine, Hyoscyamine, Stramonium, Belladonna, and Rabellon are the time-honored medicaments for Parkinsonism (Charcot refers to the use of Belladonna and Hyoscyamine in his 1877 text on diseases of the nervous sytem); these are still of definite value. In about the last 15 years the synthetic products mentioned above have become available. The best of the anti-spasmodics have included Artane, Pagitane, and Cogentin. The antihistaminics in common use have included Benadryl and Thephorin and the synthetic cerebral stimulants (Dexedrine and Benzedrine) have found some use in the specific treatment of the lethargy and akinesia of Parkinsonism.



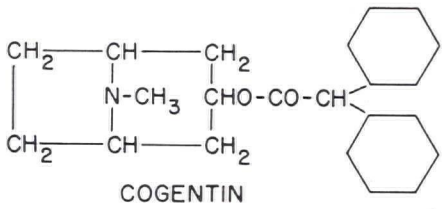
ATROPINE



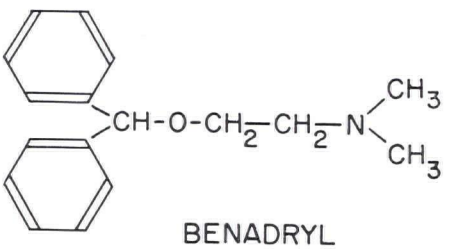
TRASENTINE



ARTANE



COGENTIN



BENADRYL

Figure 1

Structural formulas of some anti-Parkinson drugs; note similarities (see text).

A few general rules should be remembered in the use of these agents: 1. Caution in dosage with any of these drugs in the older patients; heavy dosage may lead to excessive drowsiness or excitement, confusion or hallucinations, gastrointestinal disturbances. 2. Each drug deserves use up to tolerance before switching to another. 3. Combinations of drugs may be best—as for example, giving Artane for rigidity and central stimulation along with Hyoscine or Benadryl for tremor. 4. Atropine is a suitable choice for rigidity in the young, but is *never* to be used in the old because of the threat of glaucoma. 5. The most frequent side effects to be watched for in the use of many of these drugs—dryness of the mouth and blurring of vision. 6. In general, post-encephalitic types have tremendous tolerance for any drugs, arteriosclerotic types have least tolerance. 7. Artane or Pagitane are usually good drugs with which to start and, in general, are safe enough for any age group. 8. Spectacular initial response is not too unusual, but probably will "wear off" in time. This same response, though usually less spectacular, may be repeated on shifting to other drugs. 9. Hence, rotation of drugs is to be borne in mind in the care of these chronic patients. 10. Some of these drugs seem to have rather selective action—for example, for rigidity, Atropine, Artane, or Cogentin seem best; for tremor, Hyoscine, Benadryl, or Stramonium; for akinesia, Dexedrine or Artane; for oculogyria, Artane, Pagitane, or Atropine.

It is interesting to note that the *"old"* potato plant products and the *"new"* synthetics (both anti-spasmodics and anti-histaminics) bear some definite similarities in chemical structure (see structural formulas illustrated); hence their fairly similar effectiveness in Parkinsonism should come as no great surprise. Trasentine, developed during the 1930's in a search for a synthetic Atropine-like drug, was itself ineffectual in Parkinsonism but became the prototype of Artane and other effective synthetic anti-spasmodics. Interestingly, though, this same Trasentine which sparked the development of all the synthetic anti-spasmodics bears an even stronger chemical structural resemblance to Benadryl, the anti-histaminic (q.v.), than it does to Artane! This trend of chemical similarities in effective anti-Parkinson drugs is epitomized by Cogentin in that it combines the "virtues"—in this case, the active radicles—of Atropine (peer of the old potato plant products) and Benadryl (the anti-histaminic).

In connection with Cogentin, Himwich and Rinaldi[5], and other collaborators have done some interesting work lately in determining the site of action of this and related drugs. In studies on rabbits, they have found that Cogentin and other effective anti-Parkinson drugs seem to work at the level of the reticular system (a cholinergic system), by their anti-cholinergic action reducing or eliminating both the upstream as well as downstream effects of the activating system. Himwich points to this as a possible explanation for both the subjective and objective improvement in Parkinsonism patients on these drugs—in effect, a pharmacological lobotomy (diminishing the upstream arousal stimuli from the brain stem reticular formation) and a pharmacological tractotomy of the reticulo-spinal tracts (diminishing the downstream effect of theoretically 'released' extrapyramidal efferents). In this last, Himwich's theory clearly embraces the ideas of Jenkner and Ward and Falkerts and Spiegel described above. From this experience, Himwich has further suggested using the reticular activating system in this way for screening anti-Parkinson drugs developed in the future.

This has been a glimpse of Parkinsonism in 1958, one hundred and forty-one

years after James Parkinson wrote, with undaunted optimism and with words that still apply, "but, although, at present, uninformed as to the precise nature of the disease, still it ought not to be considered as one against which there exists no counter-vailing remedy" and then added, in saluting future investigators, "by their benevolent labours, its real nature may be ascertained and appropriate modes of relief, or even of cure, pointed out".

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