Therapy of Parkinson's Disease

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SUMMARY

The most disabling form of Parkinsonism is that occurring after encephalitis. It may occur in persons of any age. The results of surgical treatment, which has been used for the most part only for seriously handicapped patients, have been discouraging in general, although in a few isolated circumstances operation has been of dramatic benefit.

The solanaceous alkaloids—atropine, stramonium and hyoscine—either in pure forms or in mixed extracts or tinctures — are the best established drugs at present for the treatment of the postencephalitic forms of Parkinsonism. They have not proven too helpful for patients in the older age group with paralysis agitans. The antihistaminic compounds, particularly Benadryl,® have been a very valuable addition. They are of greatest value for patients in the older age group. The newer synthetic compounds, Artane® and Panparnit,® are also valuable additions. Amphetamine and the related and subsequently produced agents in this group are very helpful for patients showing undue fatigue and lethargy. Tolserol® is proving helpful, particularly for patients with painful spasms of rigid muscles.

IN a review of the literature it was noted that paralysis agitans of the degenerative or arteriosclerotic type appearing late in life seemed to be most commonly commented upon.

Beginning in 1917, just 100 years after James Parkinson had described the disease as a syndrome, and particularly during the winters of 1918 through 1920, serious attacks of epidemic encephalitis occurred. Following this pandemic numerous manifestations of a syndrome resembling paralysis agitans occurred. This latter syndrome is now referred to as postencephalitic Parkinsonism. The postencephalitic form differs from the classic description by Parkinson in that persons of any age may be affected and there are many associated symptoms which make the condition more disabling. Most investigators[7, 10] consider paralysis agitans and Parkinsonism as synonymous and group them under three general headings: Postencephalitic, idiopathic, and arteriosclerotic. The syndrome is occasionally observed in toxic, neoplastic or post-traumatic states. While rare, these conditions must be considered in differential diagnosis.

Basically the disease is an involvement of the extrapyramidal portion of the central nervous system.[3, 4, 5] It varies in intensity and extent throughout the structures of this system. Owing to lack of knowledge of the anatomy and physiology of the structures, the pathophysiological disturbances of this disease cannot be concisely explained. The most common sites of pathologic change are the globus pallidus, the putamen and the substantia nigra. The cortex is less frequently involved, and the corpus Luysii and the red nuclei only occasionally. Recent investigators have been directing their attention to the reticular substance, and in all probability this latter locus will prove to be an important area for study and understanding.

The commonly observed signs are: Increased muscle tonus (rigidity), tremor of rest, flexed posture and festination of gait—the classical picture of paralysis agitans. Persons with the postencephalitic form of the disease have, in addition, increased salivation, oily skin, oculogyric crisis, and reversals of sleep rhythms. Psychic disturbances occur and must be considered in all therapeutic programs. As in all chronic illnesses, discouragement and depression are common. The psychic symptoms at times become very distressing or disabling. This is particularly true in younger persons in whom behavior disorders are often the only evidence of the disease. As the patient's intellect is seldom affected, psychotherapy is important.

Parkinsonism can be classified as mild, intermediate or severe. In the mild cases, quite often the patient is more comfortable on a good hygienic regimen than with medication. The side-reactions accompanying the use of drugs are quite often so distressing that the patient with mild Parkinsonism would prefer getting along without drugs. The greatest opportunity to aid with medication exists in the intermediate group.

TREATMENT

The first attack upon this problem should therefore be directed toward psychic rehabilitation and maintaining physical strength and vigor in the patient. It is wise to avoid terms alarming to the patient—terms such as "shaking paralysis," "creeping paralysis," and "sleeping sickness." It is far better to emphasize the slowness of progression of the disease and to reassure the patient in any possible manner. Often this entails a reordering of the patient's life. As mental or physical fatigue intensifies the symptoms, activities should be planned accordingly. There should be a moderate amount of

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outdoor activity. As the rigid muscles respond to heat, physiotherapy in the form of baking and massage is indicated. For patients with muscle spasm, a warm bath before retiring may be helpful.

The postencephalitic form is a sequel to epidemic encephalitis. It may, but rarely does, follow other forms of encephalitis. As knowledge of the anatomy and physiology of the nervous system has developed, surgical approaches to the problem have been made. Areas 6 and 4S have come under scrutiny and some investigators have ablated these areas. At first the results were promising, but in most instances the symptoms returned after recovery from the initial shock of operation. Other areas and tracts have been ablated, with questionable results. Perhaps the greatest surgical success has been achieved in relief of postencephalitic hyperpnea;[8] section of the phrenic nerve relieved the distressing symptoms and restored totally incapacitated patients to reasonable comfort. With an increase of knowledge in the field of neurophysiology as pertains to the extrapyramidal system, it is probable that neurosurgeons will devise means more suited to individual cases. Certainly, attempting surgical relief in severe cases is justified, and the information thereby obtained may permit more rapid advance in all fields of therapy. At present, palliative treatment is about all that is available for the patient with severe Parkinsonism.

The antispasmodic drugs of the solanaceous alkaloids[9] have been, and probably remain, the most useful therapeutic agents. The main alkaloids used are atropine, scopolamine, and stramonium. The early investigators tended to use small doses, but with more experience it was found that massive dosage was necessary. In mild cases the side-effect of mydriasis and the drying up of the saliva was more distressing than the moderate muscular rigidity. It was observed that patients with intermediate Parkinsonism had considerable tolerance for these drugs. With the alkaloids, a minimal dose should be used at first and the dosage then increased to the point of therapeutic results or the patient's tolerance. The response of a patient to an antispasmodic drug may vary from time to time. This does not appear to be ascribable to tolerance or addiction, but rather to variations in the physiological status of the patient. The psychological benefit of changing medication is occasionally the explanation. The older tinctures and extracts were variable in potency. White wine extract has produced a more constant and therapeutically effective drug. There are several satisfactory preparations available.[2, 6, 9] Vinobel® and Rabellon® are examples. Hyoscine hydrobromide, in 0.4 and 0.6 mg. doses, three to 12 times per day, is very helpful to most patients. The greatest usefulness of this drug is in the control of oculogyric crisis. For emphasis: Therapy must be tailored to the peculiar needs of each patient and must be altered as the needs change.

Quite often patients complain of undue drowsiness, a distressing symptom of this disease. With the advent of sympathomimetic drugs (ephedrine, amphetamine),[2] it was realized that they were logical additions to the therapeutic program of these patients. From 10 to 25 mg. of amphetamine is usually given at the time the patient rises in the morning, and if necessary it is repeated around 11 a.m. It is advisable not to give this drug in the afternoon as it may interfere with sleep at night.

Thus, the alkaloids and sympathomimetic drugs constitute the pharmacological armamentarium for the treatment of this disease. The recent chemical synthesis of drugs offering better control of symptoms is a most encouraging development.

ANTIHISTAMINIC DRUGS

Benadryl,® an antihistaminic, was tried empirically by Budnitz[1] in September 1946. The results were most encouraging. Since then, various other forms of antihistaminics have been tested. In the author's experience Benadryl has proven the drug of choice. It has been most useful for patients with paralysis agitans—relaxing the tonus, reducing the tremor and drying the saliva. The alkaloids, added to the regimen, increased the benefit. Twelve patients with severe paralysis agitans were given Benadryl with alkaloids. Tonus was reduced in each case; tremor was arrested in two and reduced in eight. All the patients showed improvement in that they developed a sense of well-being. In postencephalitic patients, salivation was controlled, emotional expression improved in facial muscles, and a renewed interest in activities was noted by relatives. Benadryl is administered in 50 mg. doses, three to four times per day. The dosage of alkaloids can be reduced gradually as the patient is started on the antihistaminic.

Corbin[2] commented upon the use of a new synthetic antispasmodic agent, Artane.® The pharmacological properties of this compound have been carefully studied. It is supplied in 2 mg. tablets provided with a line for halving the dose. Most patients can tolerate a 2 mg. tablet three times a day. It is usually administered before meals and the dose gradually increased to four or five 2 mg. tablets a day. Uncomfortable side-effects are few and patients who have tolerated high atropine alkaloid doses may be given up to 10 or 15 mg. of Artane a day. The symptoms of toxic effect were reported as minor. Usually these consisted of a feeling of giddiness, unsteadiness of gait, blurring of vision, dryness of the mouth, and occasionally nausea, nervousness and tinnitus. Some patients became extremely nervous and it was reported that two patients had mild delirium. The two patients who had the most pronounced side-effects had a history of sensitivity to other drugs. In cases in which side-effects developed, use of low dosage and building up to tolerance permitted continuance of the drug. Corbin stated that the feeling of nervousness caused by Artane in some cases was controlled by the administration of phenobarbital. It has been the author's experience that most postencephalitic patients do not tolerate sedative drugs well, and for that reason changing to some other therapeutic agent is suggested.

Tolserol®[4,5] is a more recently introduced therapeutic agent which has pronounced spasmolytic effect. Its greatest usefulness is in cases in which muscle spasm and pain are present, or in which dystonic or athetoid movements are complicating factors. This drug is available in four forms: Tablet, capsule, elixir and 2 per cent solution for intravenous use. It is usually administered in doses of 1 gm., three to four times a day. The liquid form is absorbed more rapidly and has proven more satisfactory in the author's experience. The intravenous administration of Tolserol produces a rapid therapeutic level of the drug, and results can be determined in a short period of time.

In 1946, Domenjoz[3] reported pharmacological experiments with a variety of synthetic compounds related to Trasentin® and found that they had approximately one-tenth the antisecretory effect of atropine and yet were powerful antispasmodics. The least toxic and most efficient of these was Panparnit® (introduced under the name of Parpanit®). It is related to atropine and hyoscine in structural formula. Schwab and Leigh[7] reported on this drug. Their work was well controlled, the results well validated, and the action upon muscles determined by electromyelography. The drug is available in a 12.5 mg. tablet and a 50 mg. tablet. It is advised that the drug be given on the following schedule: One 12.5 mg. tablet every three to four hours for five doses during the first day, two 12.5 mg. tablets five times on the second day, three 12.5 mg. tablets five times on the third day, then, beginning on the fourth day, one 50 mg. tablet five times a day. The dosage then may be adjusted up or down according to the patient's needs. Most patients seemingly are benefited on the 50 mg. tablet regimen. It is important to note that the drug is utilized rapidly in the body, and therefore must be administered at three- to four-hour intervals to get maximum results.

When using any of the newer drugs, the alkaloids should be continued. A gradual reduction should be carried out. In many cases the patient is most comfortable if a combination of drugs is continued.

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