CLINICAL AND PHARMACOLOGICAL STUDIES IN POST - ENCEPHALITIC PARKINSONISM

A Thesis submitted to the University of Glasgow
in candidature for the degree of

Doctor of Philosophy
in the
Faculty of Medicine

by

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SUMMARY

CLINICAL AND PHARMACOLOGICAL STUDIES IN POST-ENCEPHALITIC PARKINSONISM.

Chapter I. General Introduction

This chapter deals mainly with the control of skeletal muscle tone and the physiology of tremor. The clinical features and treatment of Parkinsonism are also discussed.

Chapter II. Crises in Post-Encephalitic Parkinsonism

A study of 67 patients with post-encephalitic Parkinsonism revealed three types of crises: they can be described as oculogyric, sweating and breath-holding.

The clinical accompaniments of oculogyric and sweating crises are described. Attention is drawn to the vasomotor changes which occur during severe oculogyric and sweating crises and to changes in mood during oculogyric crises.

The pathogenesis of the oculogyric crisis is discussed. It is suggested that ocular deviation is the consequence of a vestibulo-ocular reflex in patients with brain stem lesions involving the vestibular pathway. The emotional changes which accompany oculogyric crises are probably the result of stimulation of the diencephalon.

The role of emotion in precipitating oculogyric crises is confirmed. When emotion is known to play a part, it is suggested that the mechanism includes a conditioned reflex. Alternatively it may be /

be that the onset of emotional disturbance sometimes permits activity in the vestibulo-ocular reflex; activity which in the non-emotional state is materially inhibited.

Chapter III. Drug Therapy in the Crises of Post-Encephalitic Parkinsonism

The treatment of severe oculogyric and sweating crises in 11 patients with post-encephalitic Parkinsonism has been studied.

The value of 200 mg. sodium phenobarbitone given intramuscularly or sodium amylobarbitone 200 to 300 mg. given orally was assessed. Neither of these forms of treatment affected the natural course of crises when these were in the category classified as "severe".

A therapeutic trial was carried out to evaluate sodium phenobarbitone 150 mg. given intravenously and 50 mg. given intramuscularly in severe crises, using injections of normal saline as the control. Relief was obtained in 20 to 40 minutes after these injections of the barbiturate. Injections of normal saline were ineffective. It is suggested that in severe crises sodium phenobarbitone injected intravenously is the treatment of choice. Although parenteral injections of hyoscine hydrobromide is effective in controlling severe oculogyric crises, the use of intravenous sodium phenobarbitone is to be preferred. The use of parenteral injections of atropine sulphate is not recommended.

The prophylactic value of sodium phenytoin was determined in 5 patients suffering from severe oculogyric crises. This drug altered the /

the character of the oculogyric crisis but did not reduce its frequency or severity.

The writer has no experience of oculogyric crises induced by drugs of the phenothiazine series such as Perphenazine, but there appears to be a prima facie case for the intravenous injection of sodium phenobarbitone in this type of medical emergency.

Chapter IV. The Electroencephalogram in Post-Encephalitic Parkinsonism

Electroencephalographic study of 30 patients suffering from post-encephalitic Parkinsonism showed that over half of them have low voltage alpha rhythms (below 40 μv.). It would appear that in post-encephalitic Parkinsonism the phenomenon of low voltage E.E.G.s is most frequently seen in patients who are known to be liable to oculogyric crises and in those who suffer from severe rigidity and who are incidentally often bedfast.

There was a very high incidence of theta activity most prominent frontally. The records of 9 patients were regarded as definitely abnormal because of the presence of high voltage theta and delta activity. Abnormal records were more common in patients who suffer from severe rigidity.

The E.E.G. during an oculogyric crisis has the following characteristics: anteriorly there are high voltage spike potentials, in the other areas there is a general lowering of voltage, beta activity may become /

become more obvious.

Administration of 1.5 mg. of prostigmin intramuscularly had little or no effect on the E.E.G.

Chapter V. Deformities in Post-Encephalitic Parkinsonism

The deformities of the hand in post-encephalitic Parkinsonism have been classified as Types I, II and III. Type I (main d'accouchement deformity) is the most common form.

Talipes equino varus deformity is the common deformity of the foot in Parkinsonism.

Scoliotic deformity of the spine, especially of the cervical spine, is common. The scoliosis is usually concave to the less rigid side.

The factors of importance in the pathogenesis of deformities include: skeletal muscular weakness, rigidity and involuntary muscle spasms. Muscle weakness is the most important factor. It is emphasised that deformity is not due to the action of the rigid muscles (as is commonly thought), but results from an uncounterbalanced action of the stronger and less rigid muscles. The opposing weaker and more rigid muscles are lengthened as a result.

It is suggested that the effect of posture is probably the most important factor responsible for dribbling of saliva.

The use of splints and lamb's-wool in the management of some types of deformities is discussed.

Chapter VI. /

Chapter VI. Assessment of Drug Therapy in Parkinsonism

The relative therapeutic value of orphenadrine and "UK. 738" (Sandoz) were studied by means of a double blind trial. Orphenadrine 100 mg. thrice daily was found to be about three times as effective as "UK. 738" 4 mg. t.d.s.

The methods of assessment of the efficacy of drug therapy in Parkinsonism are reviewed and the value of objective measurements is demonstrated. It can be said that the results of objective measurements usually run roughly in parallel with an assessment of the patient's condition as determined by the clinician - and especially when the initial degree of disability is moderate.

By means of "acute" experiments it was shown that after oral administration of orphenadrine, peak activity occurred in about two hours whereas peak activity due to benzhexol occurred in two to three hours. It was not possible to demonstrate clearly defined peak activity for the drug "UK. 738". Failure to carry out the objective tests at the time of maximal activity of drugs is an important source of fallacy in clinical trials designed to assess the relative merits of preparations used to combat the disabilities associated with Parkinsonism.

Chapter VII. The sites and mode of action of orphenadrine and other drugs used for the relief of rigidity and muscle weakness in Parkinsonism

Pharmacological /

Pharmacological studies with orphenadrine show that it has a definite neuromuscular blocking action in the frog and in the rat. In the cat, however, the neuromuscular blocking action is very much less. It is suggested that one of the ways by which orphenadrine reduces Parkinsonian rigidity is through its peripheral skeletal muscular relaxant property. The euphoric action noted in human subjects and the peripheral skeletal muscular relaxant property contribute to the favourable effect of this drug on the muscle weakness and easy fatiguability in patients suffering from Parkinsonism.

Benzhexol and "UK. 738" do not possess a neuromuscular blocking action. Ethopropazine, on the other hand, shows a neuromuscular blocking action in the rat. It is possible that one of the ways whereby ethopropazine relieves rigidity is through its peripheral skeletal muscular relaxant action.

It is the opinion of the writer that a depressant action on the cerebellum is probably one of the ways by which benzhexol relieves the rigidity of Parkinsonism.

In the cat, orphenadrine antagonises the neuromuscular block induced by suxamethonium. This suggests the possible use of orphenadrine as an antidote to suxamethonium when the latter has caused complete and prolonged neuromuscular block in human subjects. It is also suggested that orphenadrine may be of therapeutic value in the prevention of muscle pain after the administration of suxamethonium.

PREFACE

Early in 1959, the two post-encephalitic wards in Stobhill General Hospital came under the care of Professor Stanley Alstead. As a post graduate research student in the Department of Materia Medica and Therapeutics I was invited to investigate some of the problems of Parkinsonism as presented by the 67 patients who were accommodated in the two wards.

This Thesis is based on the experience gained while looking after the patients over a period of nearly three years. Inevitably, all sections of the Thesis reveal the viewpoint of the clinician concerned with the natural history of Parkinsonism and the therapeutic measures commonly used for the relief of patients afflicted by this disease. The main parts of the Thesis are concerned with the following problems: the crises of post-encephalitic Parkinsonism and their treatment; deformities in Parkinsonism and their management; assessment of drug therapy in Parkinsonism; and the mode of action of drugs used for the relief of rigidity and muscle weakness in Parkinsonism.

It is intended that this Thesis should bring together in one volume a study of many problems characteristic of Parkinsonism and the methods of dealing with them.

ACKNOWLEDGMENTS

I have great pleasure in recording my thanks to many people who have helped me in the preparation of this Thesis.

I am much indebted to Professor Stanley Alstead, Regius Professor of Materia Medica and Therapeutics, University of Glasgow, for giving me the opportunity to study patients under his care. He has shown continuous interest in this work and has guided me throughout the period of study. I am obliged to him for checking all sections of the Thesis in the draft form and offering criticisms and suggestions to clarify the presentation of results. I was glad to act on his suggestion that sodium phenobarbitone should be given parenterally in the treatment of severe Parkinsonian crises.

In 1960 I was appointed to the post of Registrar (attached to Professor Alstead's Unit) by the Western Regional Board and I am grateful to the Board for their confidence in me and for the financial help derived from this appointment.

I am grateful to Mr. J. J. Lewis, Senior Lecturer in Experimental Pharmacology in the University of Glasgow for the guidance I received from him while I was working in his laboratory; Mr. Lewis also read Chapter VII and made helpful suggestions and criticisms. Also through the good will of Mr. Lewis I was helped in various ways by Dr. K. Ahmad, Mr. T. Muir, B.Sc., and Miss F. M. Carey, B.Sc. Miss Gladys Marren gave me technical assistance and printed most of the photographs.

I /

I am indebted to Dr. J. G. Macarthur for his independent advice on the presentation of Chapter VII; to Dr. I. A. Boyd, Department of Physiology, University of Glasgow, for his criticism of the section dealing with the structure and functions of the muscle spindles; and to Dr. J. C. Brocklehurst (who was closely associated with me in the earlier stages of this work) for his interest and suggestions.

My thanks are also due to Dr. S. Renfrew in the Department of Neurology and Electrophysiology at the Royal Infirmary, Glasgow and to his staff - especially Mrs. I. Johnstone (Chief Technician) - for recording the electroencephalograms. The circumstances made this part of the work excessively arduous, and I am correspondingly grateful for the trouble that was taken to enable me to complete this part of the investigation. I received much help from Dr. Renfrew and his staff in the interpretation of the E.E.G.s, and Dr. Renfrew kindly read Chapter IV and offered constructive criticism.

I wish to thank Mr. P. Waldie (Medical Photographer, Stobhill General Hospital) and his staff and also Mr. R. Callander (Medical Artist, University of Glasgow), for their help with some of the photographs and line drawings.

Responsibility for the medical care of this large number of post-encephalitics for nearly three years has provided me with valuable experience in the management of patients with chronic disabilities which have led to segregation. I should like to pay tribute to the skill and devotion of the nursing staff whom I have seen at work day by day, and I must emphasise the fact that the nurses' care under the /

the supervision of Sister E. Biggam and Sister M. Quigley was indispensable to the prosecution of this research. The insight which many of the sisters and nurses possess into the manifestations of Parkinsonism is remarkable and is of the greatest value to the research worker. I also wish to record my thanks to the patients themselves for their sustained co-operation - even when this necessitated periods of discomfort and exacerbation of symptoms.

I am grateful to Miss M. Muir for the painstaking work she has performed in typing this Thesis.

Finally, I am indebted to the following manufacturers who have kindly supplied drugs needed in the course of this work:

1. Messrs. Sandoz Products Limited for supplying various preparations of N-ethyl-nortropine benzhydryl ether bromide (UK. 738).

2. The Camden Chemical Co., Ltd., for supplying orphenadrine hydrochloride.

3. Messrs. Lederle Laboratories, London, for supplying benzhexol hydrochloride.

4. Messrs. May and Baker, Dagenham, for supplying ethopropazine hydrochloride.

LIST OF PUBLICATIONS

Certain aspects of the work described in this Thesis have been published. The publications are as follows:

(1) Drug therapy in the crises of post-encephalitic Parkinsonism.

Scot. med. J. (1961). 6, 368.

(2) Crises in post-encephalitic Parkinsonism.

Brain (1961). 84, "In press".

In addition, part of this work has been communicated at the following meeting:

British Pharmacological Society in Edinburgh, in July, 1961 - Assessment of drug therapy in Parkinsonism.

MATERIALS

The names of certain drugs have been abbreviated as follows:

1. Orphenadrine hydrochloride is described as Orphenadrine
2. Benzhexol hydrochloride " " " benzhexol
3. Ethopropazine hydrochloride " " " ethopropazine
4. N-ethyl nortropine benzhydryl ether hydrobromide " " " UK. 738
5. Atropine sulphate " " " atropine
6. Hyoscine hydrobromide " " " hyoscine
7. Tubocurarine hydrochloride " " " tubocurarine
8. Suxamethonium iodide " " " suxamethonium
9. Neostigmine methyl sulphate " " Neostigmine or prostigmin
10. Adrenaline hydrochloride " " " adrenaline
11. Noradrenaline hydrochloride " " " noradrenaline

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1. /

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CHAPTER I.

GENERAL INTRODUCTION

DEFINITION OF PARKINSONISM

In 1817, James Parkinson (1755 - 1824), a general practitioner working in Shoreditch, near London, published an account of six cases of what he called "The Shaking Palsy". This is still regarded as one of the classic monographs of medical literature. Parkinson deplored the practice, common at that time, of lumping together miscellaneous diseases characterised by tremor; and he identified a syndrome which included tremor and muscle weakness. He pointed out that the involuntary tremor is present at rest, disappears when the patient is executing movement but reappears when the movement is completed.

Although Parkinson did not mention rigidity as one of the cardinal signs of the shaking palsy, the term Parkinsonism is now used as an eponym to describe the clinical syndrome which consists of rigidity, involuntary tremor and weakness. This term is a very useful one from the therapeutic point of view for it brings together conditions which are of different aetiological origin but may respond to the same forms of therapy.

AETIOLOGY OF PARKINSONISM

Since Parkinson described the clinical features of the shaking palsy (paralysis agitans) the aetiology of Parkinsonism has been of profound /

profound interest to anatomists, physiologists, pathologists, physicians, and also to pharmacologists. Parkinson was unable to find a cause. It is now known that Parkinsonism can be due to a variety of causes, viz., cerebral arteriosclerosis (Critchley, 1929); as sequels of encephalitis lethargica (Von Economo, 1917; Buzzard and Greenfield 1919; and Bramwell and Miller, 1920); secondary to tumours of the brain (Sciarra and Sprofkin, 1953; Oliver, 1959; David and Rebufat, 1960); hepatolenticular degeneration (Wilson 1912; Barnes and Hurst, 1925); manganese poisoning (Charles, 1927); carbon monoxide poisoning (Shillito and associates, 1936); syphilis of the mesencephalon (Wilson and Cobb, 1924); Behcet's Syndrome (Pallis and Fudge, 1956; Wadia and Williams, 1957); traumatic injuries (Patrick and Levy, 1922; Walker, 1937).

ANATOMY, PHYSIOLOGY AND PATHOLOGY

PATHOLOGY

Parkinson made no post mortem studies but suggested that the disorder was attributable "to a diseased state of the medulla spinalis, in that part which is contained in the canal formed by the superior cervical vertebrae, and extending as the disease proceeds, to the medulla oblongata." This suggestion was made because the tremor usually started in the upper limbs and as the disease progressed the lower limbs and later the muscles of speech and deglutition become involved. /

involved.

Much of the relevant early literature on the pathology of Parkinsonism has been reviewed by Greenfield (1955). It is desirable however to draw attention to a number of publications which were of special importance in establishing the correct localisation of the pathological lesions in Parkinsonism. One of the first reports on the pathology of paralysis agitans was by Blocq and Marinesco who reported a case of unilateral Parkinsonism (Blocq and Marinesco, 1894). This was a man of 38 who had a tuberculoma the size of an olive in the right half of the midbrain destroying principally the substantia nigra. There was no destruction of the cortico-spinal tract. Holmes (1904) described cases with hemiparesis but showing rigidity and tremor of the Parkinsonian type. In two cases, post-mortem examination revealed tumours of the midbrain which had destroyed the red nucleus with degeneration of the rubospinal tract. The substantia nigra was also destroyed. In 1912 Kinnier-Wilson (Wilson, 1912) published his now classic paper on hepatolenticular degeneration. The most significant lesion in the brain was cystic degeneration of the putamen. Lewy (1913) reported on the pathological examination of 60 cases with idiopathic paralysis agitans. His main findings were the great shrinkage of the lenticular and caudate nuclei with loss of cells and evidence of gliosis. In addition he found peculiar inclusion bodies (now known as Lewy bodies) in the dorsal nucleus of the vagus and in the nucleus of the ansa-lenticularis. Hunt (1917) reported /

reported on the pathological changes in juvenile Parkinsonism. The principal findings were the atrophy and diminution in the number of ganglion cells in the caudate nucleus and the putamen. There was also an increased gliosis and a thinning of the fibres of the stria-hypothalamic radiations.

During the last epidemic of encephalitis lethargica several post mortem reports were published (von Economo, 1917; Wilson 1918; Marie and Tretiakoff, 1918; Buzzard and Greenfield, 1919; Bramwell and Miller, 1920; Boyd, 1915; McAlpine, 1926; Keschner and Sloane, 1931). Patients who died in the acute phase showed widespread changes in the brain, but the midbrain was usually the part most commonly affected; and the periaqueduetal zone being most severely involved. The principal pathological changes were perivascular infiltration with cells usually of the lymphocytic type. There was congestion of the brain with scattered haemorrhages and venous thrombosis. The brain tissue was oedematous; there was proliferation of the neuroglia and also cellular infiltration of the tissues especially around the cranial nerve nuclei in the pons and midbrain. In the chronic stage the most conspicious lesion was degeneration and shrinkage of the substantia nigra with great loss of cell mass. Other parts of the brain stem and the basal ganglia might show changes, but again the midbrain appeared to bear the brunt of the disease. The correlation of the clinical syndrome called Parkinsonism with pathological findings of this type is regarded as conclusive evidence that the /

the disease is attributable to lesions of the basal ganglia and the brain stem and especially the midbrain.

ANATOMY

This will be described very briefly and attention will be paid mainly to the fibre connections of the nuclear masses involved.

The following nuclear masses are involved in the production of Parkinsonian rigidity - the corpus striatum and the substantia nigra.

The substantia nigra is a layer of grey matter containing numerous deeply pigmented multipolar nerve cells. It is situated in the midbrain and in transverse section lies between the basis pedunculi and the tegmentum of the midbrain. The fibre connections have not yet been fully defined, but by means of embryological and histological studies Cooper (1946) identified the following connecting fibres:

(1) Nigro-peduncular fibres to the cerebral peduncles.

(2) Nigro-tegmental fibres directed from the caput of the substantia nigra to the red nucleus, the lemnisci and posterior longitudinal bundle.

(3) Intra-nigral links.

(4) Subthalamo-nigral intercommunications.
These appeared to be very rich.

(5) Inter-nigral links.

(6) Optico-nigral links from the optic tract to the substantia nigra taking the transpeduncular route.

Cooper /

Cooper did not find or mention any connections with the pallidum, but Ranson and Ranson quoted by Martin (1959) and Glees and Wall (1946) claimed to have demonstrated communicating fibres from the substantia nigra to the globus pallidus of the lentiform nucleus.

The Lentiform Nucleus

This nucleus with the caudate nucleus, amygdaloid and subthalamic nucleus of Luys and the claustrum constitute the basal ganglia.

The lentiform nucleus, as its name implies, is shaped like a biconvex lens, but the curvature of its medial surface is greater than the curvature of the lateral surface. The cut surface shows that it consists of two portions which differ in colour. The larger lateral portion, which is dark in colour, is the putamen; the smaller medial portion is of a lighter tint and is termed the globus pallidus (Johnston and Whillis, 1944).

Fibre connections (see Fig. 1).

(a) From the globus pallidus. The following important connections are known to exist (Ranson, Ranson and Ranson, 1948):

(1) The ansa-lenticularis and fascicularis. These arise from the internal division of the globus pallidus and unite to form a single bundle which run into the hypothalamus; the majority of the fibres however run to the nucleus ventralis anterior of the thalamus.

(2) The pallido-subthalamic fibres from the external division of the globus pallidus. They run medially /

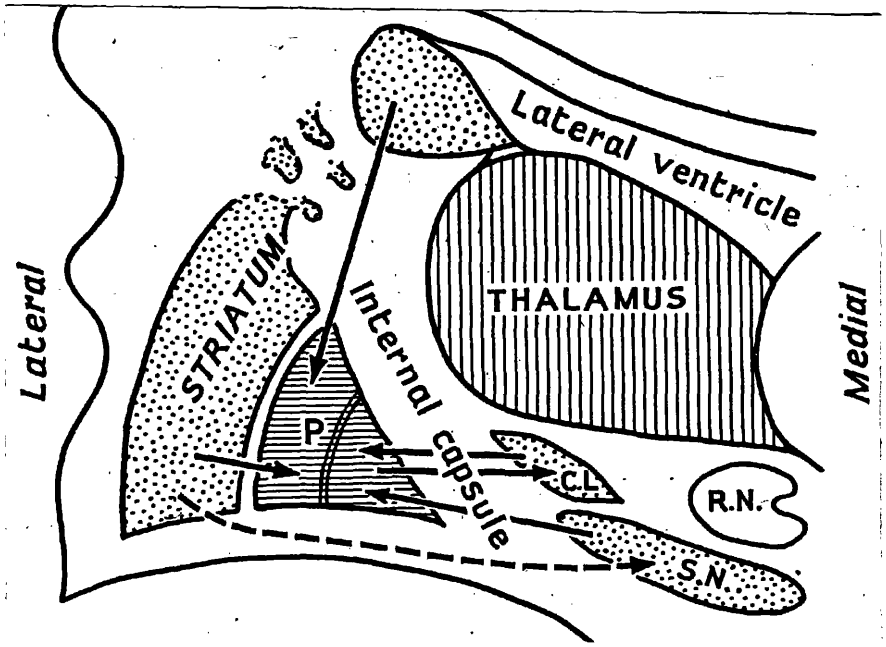


Fig. 1a. Diagram of a vertical section to show the relationship of the globus pallidus (P.) to the striatum, corpus luysii (C.L.) and substantia nigra (S.N.) and the fibre connections within this group of ganglia. R.N., red nucleus. After Martin (1959).

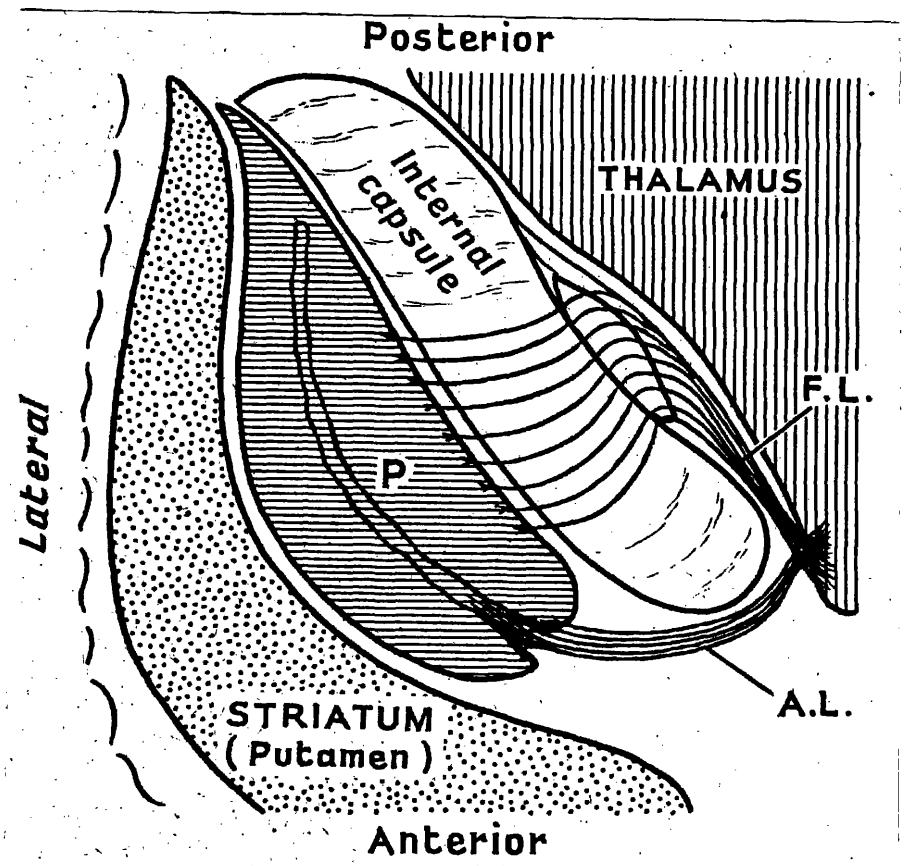


Fig. 1b. Diagram of a horizontal section to illustrate the "long" efferent fibres of the globus pallidus. F.L., fasciculus lenticularis; A.L., ansa lenticularis. Both these bundles of fibres end in the ventral part of the thalamus. After Martin (1959).

medially crossing the ventral end of the internal capsule to enter the subthalamic nucleus.

(b) The putamen gives rise to fibres which run into the globus pallidus but does not seem to contribute to the ansa or fasciculus lenticularis.

In addition to the fibres mentioned above, there are intermuncial fibres which connect the caudate nucleus and the putamen to the globus pallidus.

PHYSIOLOGY.

Parkinson's disease is classified as a disease of the extra-pyramidal system - as distinguished from disorders attributable to lesions in the pyramidal tracts.

It is generally agreed that there are two motor systems - one utilising the pyramidal tract and the other utilising the extra-pyramidal pathway. There has been considerable controversy as to the adequacy of the term "pyramidal tract" (Walshe, 1942; Nathan and Smith, 1955; Bucy, 1957 and Walsh, 1957). The term "pyramidal tract" seems to have originated from two discoveries: first is that of Betz, who in 1874 described large pyramidal cells - giant cells, situated in the neighbourhood of the fissure of Rolando and in the paracentral lobule; and secondly, the phenomenon of electrical excitability of the cerebral cortex described by Fritsch and Hitzig in 1870. It was shown soon afterwards that motor activity can be produced by stimulating the pre-Rolandic area which was named the "motor cortex" or the "motor /

the "motor area". It was thought that all the fibres in the medullary pyramid arose from the motor area or Area 4 (Fulton 1937).

Kennard and Fulton (1933) showed that there was a difference between the results of excision of Area 4 (the motor area) and Area 6 (the premotor area). Ablation of Area 4 caused flaccidity whereas ablation of Area 6 resulted in plastic rigidity. Fulton (1937), in a review, concluded that the Betz cells gave rise to the pyramidal tract, but that Area 6 contained practically no Betz cells and that its fibres led into the substantia nigra, red nucleus, pontine nuclei, reticular substance and hypothalamus. He therefore regarded the fibres from Area 6 (or premotor area) as <u>extrapyramidal</u>.

Walshe (1942) criticised this view on the grounds that the Betz cell count fell far short of the total fibre content of the pyramids. Earlier, Levin (1936) in the monkey found that it was only the presence of Betz cells that distinguished motor areas from other parts of the cortex. He found that down to the level of the pons, fibres from the premotor and motor areas were intermixed. Thus on purely topographical grounds the pyramidal fibres (from Betz cells) and extra-pyramidal fibres from premotor area, etc., down to the level of the pons, could not be differentiated from one another. Minckler and Klemme (1943), Minckler, Klemme and Minckler (1944) from a post-mortem histological study of the brain and spinal cord of a man who had had his premotor cortex removed as surgical treatment for tremor and rigidity, found that the premotor fibres pass through the internal capsule 1 cm. from the /

the genu in the posterior limb; that at level of the midbrain they occupied the same position as that assigned to the corticobulbar fibres from Area 4; at the level of the medullary pyramid they occupied the same position as that assigned to the uncrossed cortico-spinal tract from Area 4.

Mettler (1944) from his study of the primate brain, came to the conclusion that practically all the heavily myelinated fibres in the pyramids of the monkey's brain arise from the part of the cerebral cortex in which the giganto-pyramidal cells of Betz are found. All the smaller fibres disappear with total cortical ablation and therefore none of the fibres in the pyramid can be attributed to an infrapallidal origin. Lassek (1952) came to somewhat similar conclusions.

Recently several areas of the cerebral cortex have been shown to have a motor function and to contribute fibres to the pyramid. The areas are the motor area II; the supplementary motor cortex of Penfield and Welch (1951) and Bates (1953); the post-central motor cortex; additional motor cortex in the temporal and occipital lobe (Walberg and Brodal, 1953). An excellent account of the various motor areas has been given by Hines (1960).

From the foregoing discussion it is clear that although the precentral motor cortex (Area 4) which contains almost all the Betz cells (pyramidal cells) is probably the main motor cortex, there are other motor areas in the cerebral cortex although their function is uncertain at the present. It is also clear that the term "pyramidal tract" (i.e. fibres in the medullary pyramids) and the tract of fibres from /

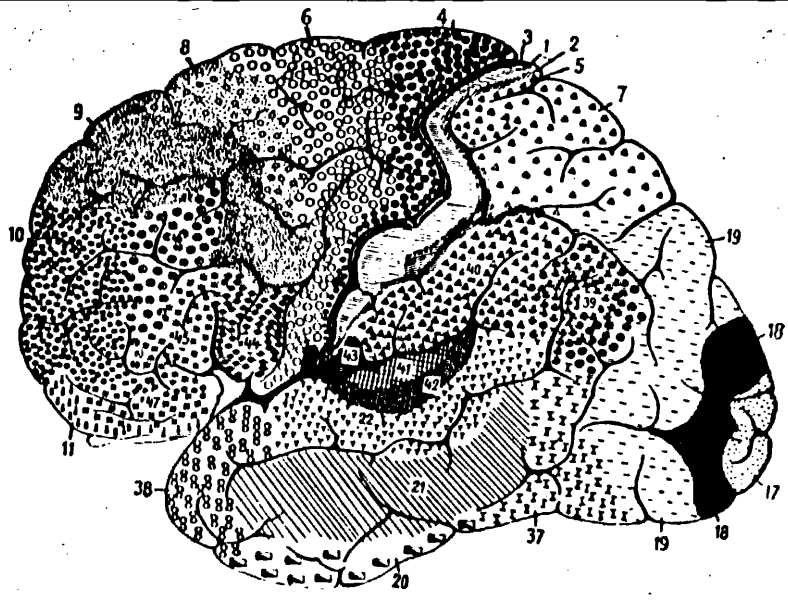


Fig. 2. Subdivisions of the cortex on the basis of cytro-architectonics. Reproduced from Walsh (1957).

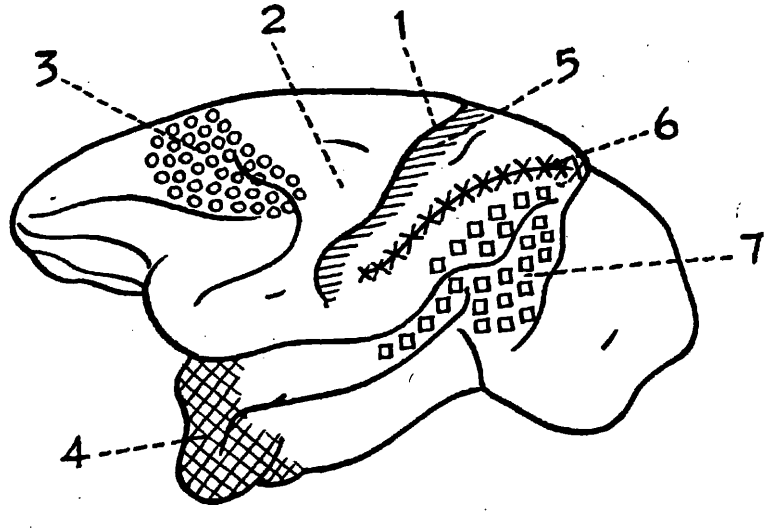


Fig. 3. Brain of the Macaque monkey showing some of the "motor areas" (Modified from Hines, 1960).
1. Fissure of Rolando; 2. Motor cortex (Area 4);
3. Extrapyramidal motor area of the frontal lobe;
4. Motor cortex of the temporal lobe; 5, 6 and 7., motor areas of the parietal lobe.

from Area 4 (i.e. from the pyramidal cells of Betz) are not synonymous and therefore the term is a misnomer. It follows that the terms "extrapyramidal tract" and "extrapyramidal system" do not have the precise topographical significance formerly attributed to them.

The Basal Ganglia

The occurrence of Parkinsonism in association with lesions of the lenticular nucleus suggests that these nuclei may be concerned with movement, particularly those instinctive and automatic movements which, in this disease, are characteristically deficient.

The corpus striatum (lentiform and caudate nuclei) is a primitive structure; it is one of the oldest parts of the cerebrum. In lower vertebrates (for example, fish, amphibia, reptiles and birds) the cortical mantle is absent or rudimentary, and the pyramidal tract has not yet come into being. In these species the corpus striatum is therefore the highest motor centre - being looked upon as homologous with the motor cortex of the higher forms (Best and Taylor, 1955). Removal of the rudimentary cortex (cortical mantle) in birds, for instance, leaves visual and auditory sensation apparently unaffected and the bird continues to carry out normal movements of feeding, courting, fighting, etc. After removal of portions of the striate body, these instinctive reactions are imperfectly executed.

Wilson (1912) observed that cystic degeneration of the putamen was associated with rigidity and tremor. He therefore proceeded to study the effect of stimulating and of destroying the lentiform and caudate /

caudate nuclei. He reported that he was unable to elucidate the functions of these nuclear masses in the primate (Wilson 1914). Later studies by other investigators showed that these nuclei served to modify movements already produced by stimulating the motor cortex or that they modified spinal reflex movements. Mettler, Ades, Lipman and Culler (1939) found that in cats and monkeys stimulation of the caudate nucleus, putamen or the claustrum inhibited movements induced by cortical stimulation, especially movements originating from the ipsilateral cortex. Stimulation of the globus pallidus imparted a factor of plastic tonus to cortically induced movements, exerted a holding effect on them and prolonged their relaxation time. Freeman and Krasno (1940) found that stimulation of the caudate nucleus inhibited spontaneous movements of skeletal muscles. Segundo, Migliaro and Rolg (1958) found that stimulation of the caudate nucleus and putamen produced either an increase or a decrease of spinal reflexes, wheras stimulation of the globus pallidus resulted only in augmentation of spinal reflexes. Earlier, Mettler and Mettler (1941) found that the inhibitory effect of the neostriatum was more marked on spontaneous activity than on cortically induced movements.

Experiments showed further that the basal ganglia are also probably concerned with the maintenance of skeletal muscular tone. Mettler and Mettler (1942) found that extension hypertonia which is produced by ablation of the cortex is short-lived and mild, but after striatal injury the extension hypertonia is much greater. Liddell and Phillips (1940) found that in cats electrolytic lesions in the basal ganglia /

ganglia (caudate and lentiform nuclei, subthalamic nucleus and claustrum) produced hypertonia which was most evident when the animal was mentally at rest and held so that the limbs hung freely. In a later study (1946) these authors found that after section of the pyramids the motor defect was minimal, but became much greater with extensor hypertonia after striatal or pallidal lesions.

In conclusion it may be said that the basal ganglia are concerned with modification of movement whether cortically or reflexly induced. They appear also to be concerned with the regulation of muscle tone.

The Substantia Nigra

The role of the substantia nigra has been difficult to elucidate by the routine stimulating and ablation procedures on experimental animals. However Mettler, Ades, Lipman and Culler (1939) showed that stimulation of the substantia nigra caused an increase in extensor tone principally of the opposite side of the body. It also produced tremor in cortically induced movements from the ipsilateral cortex. The function of the substantia nigra is not fully understood, but from clinicopathological studies it appears that this nuclear mass is concerned with the maintenance of muscle tone and with co-ordination of muscular contraction to ensure smoothness of movement.

THE CONTROL OF SKELETAL MUSCLE TONE

Hypertonicity of the skeletal muscle is an important sign in Parkinsonism and in lesions involving the "pyramidal tract". The

term "tone" is a difficult one to define but to the neurophysiologist it is that property of the muscle which causes it to resist passive stretch. This is not the same as palpable rigidity of the muscle although in most cases a palpable rigidity is associated with increased resistance to passive stretch.

There are various factors responsible for the maintenance of tone in the skeletal muscles:-

1. Spinal segmental control: It is well known that hypotonia develops when the posterior nerve roots or the posterior columns in the cord are destroyed. Thus hypotonia occurs in tabes dorsalis. The rigidity of Parkinsonism and of decerebrate rigidity are abolished or reduced by section of the appropriate posterior roots (Sherrington, 1898; Groves, 1911; Förster 1913; Pollock and Davis, 1930). Hypertonicity in "pyramidal tract" lesions is associated with increased tendon reflexes. The rigidity of Parkinsonism is, however, not necessarily associated with exaggerated tendon reflexes; in fact, the tendon reflexes may disappear when the rigidity is very gross; the hypertonic muscles are no longer in the optimum state for eliciting reflex contraction. Whether the tendon reflexes are manifestly increased or not, a definite degree of "hyper-reflexia" can be demonstrated in patients suffering from Parkinsonism by passively stretching the muscles, and especially when the passive stretching is repeated rapidly: the muscle that is being stretched contracts, and may prevent the full range of movement at the joint. Thus it may be impossible to extend fully the elbow joint in patients suffering from Parkinsonism owing /

owing to the strong contraction of the biceps brachii when this muscle is being stretched by passive extension of the elbow joint.

The maintenance of tone, therefore, depends on the integrity of the simple spinal reflex arc of which the afferent loop lies in the posterior nerve roots and in the posterior horn of grey matter. Damage to the efferent loop of the reflex arc also causes hypotonia. Thus damage to the anterior horn cells, the ventral nerve roots, or the motor nerve to a muscle results in hypotonicity (flaccid palsy).

In recent years intensive research has been carried out on the activity of muscle in health and disease. Skeletal muscle has an afferent and an efferent nerve supply. The efferent nerves have been shown to be of two types:

(1) The large alpha fibres which conduct rapidly (more than 50 metres per second) and set up the characteristic motor twitch in ordinary or extrafusal muscle fibres.

(2) The smaller or gamma efferent fibres which conduct more slowly (15-50 metres per second) and innervate exclusively the muscle spindles. Impulses from the gamma efferent fibres excite the intrafusal fibres of the muscle spindle causing it to contract and thus leading to sensory discharge from these end organs.

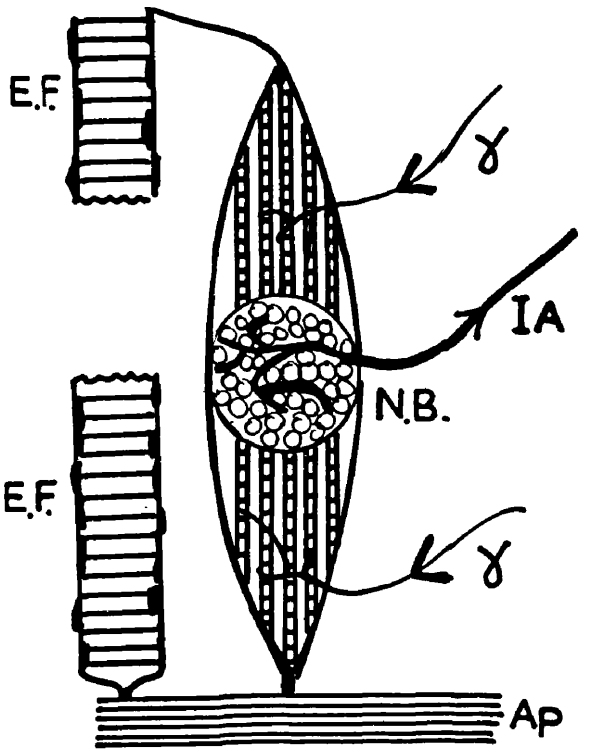
The influence of the gamma efferent nerves on reflex activity and muscle contraction has been studied by Hunt and his colleagues (Hunt, 1951; Hunt and Kuffler, 1951(a) and 1951(b)).

The structure of the muscle spindle: This has been a subject of intensive study and a helpful review of the present state of knowledge is given by Cooper (1960), and it includes some reference to recent publications by Boyd (1958, 1959).

The muscle spindle is formed by a bundle of several striated muscle fibres (the intrafusal fibres) of small size enclosed in a collagenous sheath from which they are separated by a lymphatic space in the equatorial part of the organ. The whole spindle is fusiform in shape (Fig. 4). The intrafusal fibres consist of two contractile polar regions showing a transverse striation, coarser than that of the ordinary fibre and united by a non-contractile equatorial region which is characterised by a conglomeration of nuclei which fill and distend the body of the muscle fibre. At each end of the intrafusal muscle fibre there are a number of motor nerve endings, and in the equatorial region there is a primary sensory nerve ending with or without secondary endings on either side of it.

Another type of sensory receptor lies chiefly at the junction of tendons with muscles. These sensory receptors are called tendon organs of Golgi. These are receptors of a spray form, in which the sprays lie on the surface of a tendon slip, usually close to the point at which the muscle fibres join the tendon.

Hunt and Kuffler, (1951b) have classified the afferent nerves from the muscles as A and B units according to Matthews' (1933) nomenclature. The A units - now called group IA - have a low threshold



—Muscle spindle (diagrammatic). N.B. = nuclear bag supplied by IA annulo-spiral afferent nerve. Intrafusal fibres of polar region supplied by γ efferents. Note attachment of spindle to endomysium of extrafusal muscle fibre (E.F.) at one end, and to the aponeurosis (Ap) at the other.

Fig. 4. Reproduced from Samson Wright's Applied Physiology.

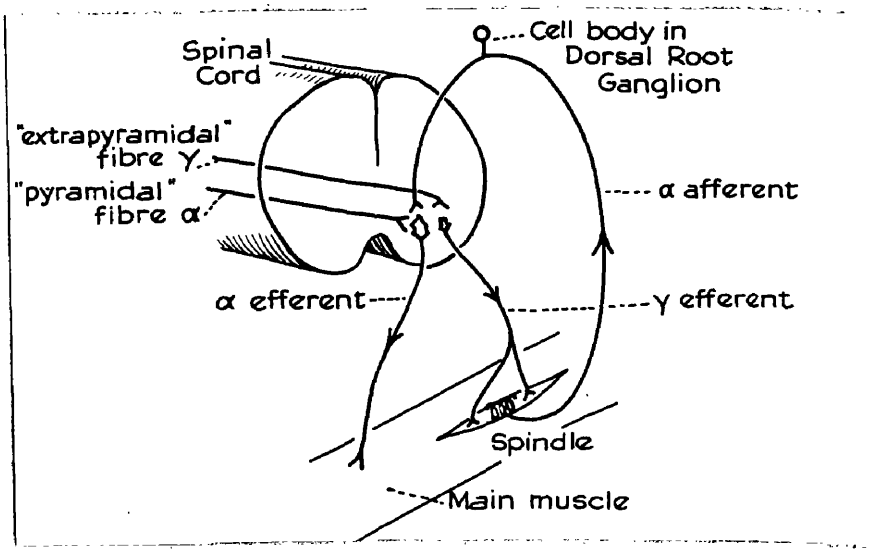


Fig. 5. Diagram to show the connections of the muscle spindle to the central nervous system.

to stretch and cease to discharge during contraction of the extrafusal fibres and originate from the muscle spindles. The B units - or group IB fibres - from tendon organs, show a higher threshold to stretch; their discharge rate is accelerated during contraction of the extrafusal fibres. No significant difference in conduction velocities were noted between IA and IB fibres indicating that impulses from both types of receptors travel in fibres of similar diameter. With regard to the role of IA and IB fibres, they suggest that IA fibres are excitatory while IB are inhibitory.

The gamma efferent fibres play an important part in the maintenance of postural tone. A large proportion of these fibres show a background discharge to resting muscles (Hunt, 1951). This background discharge is dependent on continuousness of afferent inflow from the limb into the spinal cord. If the dorsal roots are sectioned this background discharge is abolished. The afferent inflow, though derived principally from IA fibres of the muscle spindles, also comes from zones of tissue which include the skin (Hunt, 1951; Diete-Spiff and Pascoe, 1959). It is now thought that in the maintenance of postural tone the polar ends of the intrafusal fibres are activated through the gamma efferent system. The polar shortening thus induced in the intrafusal fibres causes the large spindle afferent nerves from the centre of the fibre to discharge their impulses. The afferent discharges from the spindles are said to be facilitatory for their own synergistic alpha motor neurons, and thus they cause the extrafusal

fibres /

fibres to contract and shorten.

The main muscle (extrafusal fibres) thus follows the changes in length of the intrafusal fibres (the so-called servo-mechanism of Kuffler, Hunt and Quilliam, 1951). Diete-Spiff and Pascoe (1959) suggest that for stability in such a system the length of the intrafusal fibres must be independent of the changes in the extrafusal fibres. They considered that Hunt's observation (1951) that lightly stretching the muscle results in inhibition of afferent spindle discharge, raises a major objection to the servo mechanism.

However, as already stated, there is a constant background discharge to the intrafusal fibres through the gamma efferent system. This causes afferent discharge through IA fibres (muscle spindle afferent fibres). This in turn leads to discharge through the alpha-efferent fibres, thus causing contraction of the extrafusal fibres. Kuffler, Hunt and Quilliam (1951) have shown that stretch applied to the muscle gives rise to afferent discharge through IA fibres and this again will cause the extrafusal fibres to contract. They believe that the gamma efferent system is thus well suited to act as a peripheral regulator of the proprioceptive spindle mechanism. The gamma efferents are therefore of great importance in the reflex activity of the skeletal muscle. By their activity also the muscle is maintained at fixed lengths during the maintenance of a particular postural stance.

The interaction between the two proprioceptive organs (muscle spindle and Golgi ending) produces some regulation between antagonistic muscles /

muscles of the same level. As the tension rises within a muscle in the process of contraction, the activity of the tendon endings increases and the activity of the spindle decreases. Thus monosynaptic response of the spindle is inhibited and the antagonistic response is facilitated.

The role of the gamma efferent fibres in the maintenance of tone have been demonstrated by pharmacological studies. Walshe (1924), Rushworth (1960) showed that injection of a dilute solution of procaine at the motor point of a muscle abolished rigidity in Parkinsonism although this was very short lived, lasting for only a few hours. Matthews and Rushworth (1957b) showed that in the case of a muscular nerve the gamma motor fibres were preferentially blocked by dilute procaine. Stronger solutions, however, blocked the large alpha nerves.

Pharmacological studies have also shown the role of afferent nerve fibres. Maher (1955 and 1957), Nathan (1959), Kelly and Gautier-Smith (1959) have shown that intrathecal injection of phenol can reduce spasticity and rigidity. Maher (1955), Brown (1958), Iggo and Walsh (1960) showed that the effect of the phenol is on the small afferent fibres in the posterior roots and not on the large IA fibres. Brown (1958) showed in patients relieved of their hypertonicity there was normal position and joint sense, and normal voluntary power, but there was permanent absence of deep and superficial reflexes and disturbances of postural mechanisms. It seems that the small unmedullated /

unmedullated afferent fibres - in conjunction with the control effected by the large IA and IB fibres from the muscle spindles and Golgi tendon organs - are important in the maintenance of postural tonus.

2. Supraspinal Control of Skeletal Muscle Tone.

Apart from the ill understood association between the basal ganglia and the substantia nigra and the skeletal muscle tone, it is now known that other supraspinal areas are of importance in the regulation of skeletal muscle tone. The most important of these areas is the reticular formation of the brain stem.

The reticular formation is formed of cells (and their fibres) found scattered among fibres in the lateral part of the tegmentum of the midbrain, in the dorsal part of the pons and in the medulla oblangata behind the olivary nucleus (Lockhart, Hamilton and Fyfe, 1959). The cells may be regarded as internuncial neurons with connections at the caudal and cephalic levels of the central nervous system. The cephalic connections are to the thalamus, hypothalamus, globus pallidus and the cerebral cortex. These connections have an activating influence on the cerebral cortex (Lindsley, Bowden and Magoun, 1949; Starzyl, Taylor and Magoun, 1951; French, Amerongen and Magoun, 1952): it appears that the activating effect on the cortex (as revealed in the E.E.G.) lasts for a long period (up to 30 minutes) after stopping the electrical stimulation of the reticular /

reticular formation. The segmental lesions which abolished E.E.G. activation were found to have spared large portions of the main sensory pathways.

The caudal connections consist of two tracts, first demonstrated by Papez (Papez, 1926). The tracts are the lateral and medial reticulo-spinal tracts. Our understanding of the function of these tracts is largely due to the published work of Magoun and his colleagues. Niemmer and Magoun (1947) found that the reticular formation consists of two systems - one which is inhibitory (mainly of bulbar origin) while the other is a facilitatory system and arises from each level of the brain stem. The influence of the connections from each side of the brain stem is exerted upon both sides of the cord. Magoun (1950) in an excellent review, gave the relative positions and the connections of the two systems. The facilitatory system lies lateral to the inhibitory system and is connected with Area 6, sensorimotor, associational, limbic and auditory cortical areas. The inhibitory system is connected with Areas 4S, 24S, and 19S.

Magoun and Rhines (1946) showed that in decerebrate animals all the rigidity in the extended legs was abolished when the bulbar reticular formation was stimulated. Bodian (1946) in experimental poliomyelitis in monkeys, found that spasticity appeared when the damage to the neurons began to progress from the brain stem into the upper spinal cord, and at a time when the most severe damage was in the reticular formation of the lower brain stem. This finding confirmed the inhibitory /

inhibitory influence of the reticular formation of the lower brain stem.

The role of the facilitatory system of the brain stem reticular formation in augmenting cortical motor responses was demonstrated by Rhines and Magoun (1946) and Niemer and Magoun (1947). Schreiner, Lindsley and Magoun (1949) concluded from their work that spasticity is maintained by facilitatory influx to the cord conducted via the reticulo- and vestibulo-spinal tracts. Rhines and Magoun (1946) found that the facilitating influence of diencephalic stimulation on cortically induced movements were exerted through the reticular formation of the brain stem and not through a diencephalic-cortical-spinal cord circuit as was originally supposed.

Suda Koizuma and Brooks (1958) have shown that stimulation of the reticular formation leads to descending discharges in the lateral columns of the spinal cord. More important, they showed that the reticular formation probably acts solely upon the segmental interneuron pool in producing its facilitating and inhibitory effects. Intracellular recording showed that the facilitating action of the reticular formation, though not causing the cells to "fire", permitted motor neurons not previously activated by an orthodromic or antidromic stimulation to be "fired" by such stimuli. The latency of response of other units initially taking part in the reflex was reduced by stimulating the reticular formation.

Brain stem lesions have been shown to cause exaggeration of spinal reflexes (Mettler and Zimmerman, 1943). Conditions resembling Parkinsonism have been produced in experimental animals by lesions of the /

the centromedian tegmentum (Peterson et al, 1949) and of the periaqueductal grey matter (Baily and Davis, 1944). It is of interest that lesions of encephalitis lethargica are concentrated in the midbrain with special predilictions for the periaqueductal grey matter (Wilson, 1918).

The vestibular nuclei: Fulton, Liddell and Rioch (1930) showed that experimental lesions of the vestibular nuclei in normal animals led to hypotonia on the side of the lesion. Decerebrate rigidity and the associated increased stretch reflexes are greatly diminished by lesions of the vestibular nuclei. It is now well known that decerebrate rigidity can be abolished by section of the brain stem below the level of the vestibular nuclei. Bucy (1938), however, found that section of the vestibular spinal tract in the anteromedial funiculus of the cord in spastic patients resulted only in transient reduction in the degree of spasticity. He concluded that in man, although the vestibulo-spinal tract contributed to the maintenance of spasticity, other pathways are capable of maintaining the spasticity in the absence of this tract.

The cerebellum: It is established that lesions of the cerebellum in man leads to hypotonia. It follows that the cerebellum exercises some control over the tone of skeletal muscle. This control is ipsilateral. Experimental work on animals, however, has demonstrated a facilitatory influence, which is in keeping with clinical experience (Snider and Magoun, 1949), and also an inhibitory influence on skeletal /

skeletal muscular activity reflexly or cortically induced (Snider, McCulloch and Magoun, 1949). The suppressor and facilitatory areas of the cerebellum appear to occupy largely the same areas. It has been suggested that the cerebellum may exert its influence on the skeletal muscle through the reticular formation (Sprague and Chambers, 1954; Peterson, Magoun, McCulloch and Lindsley, 1949). The latter authors go as far as to suggest that the cell of the reticular formation may act as the supraspinal interneuron cell on which impulses from the cerebrum, basal ganglia, tectum and cerebellum converge, and that through their influence on the reticular cell, the anterior horn cell is affected (Fig. 6).

The cerebral cortex: Kennard and Fulton (1933) and Fulton (1937) showed that in the monkey extirpation of Area 4 led to flaccid paralysis and that spasticity could be added if Area 6 was also ablated. Ablation of Area 6 alone gave rise to plastic rigidity. Hines (1936 and 1937) however showed that a strip of cortex now called Area 4S forming the anterior portion of Area 4 or the posterior portion of Area 6 was responsible for the addition of spasticity to the flaccid paralysis produced by ablating Area 4. Area 4S was therefore assumed to have a suppressor or inhibitory effect on skeletal muscular tone. Dusser de Baranne and McCulloch (1941) demonstrated the suppressor effect of Area 4S on the motor responses induced by stimulating Area 4. Using the method called "physiological neuronography" Dusser de Baranne (1938) showed that Area 4S is connected to the caudate nucleus and the optic /

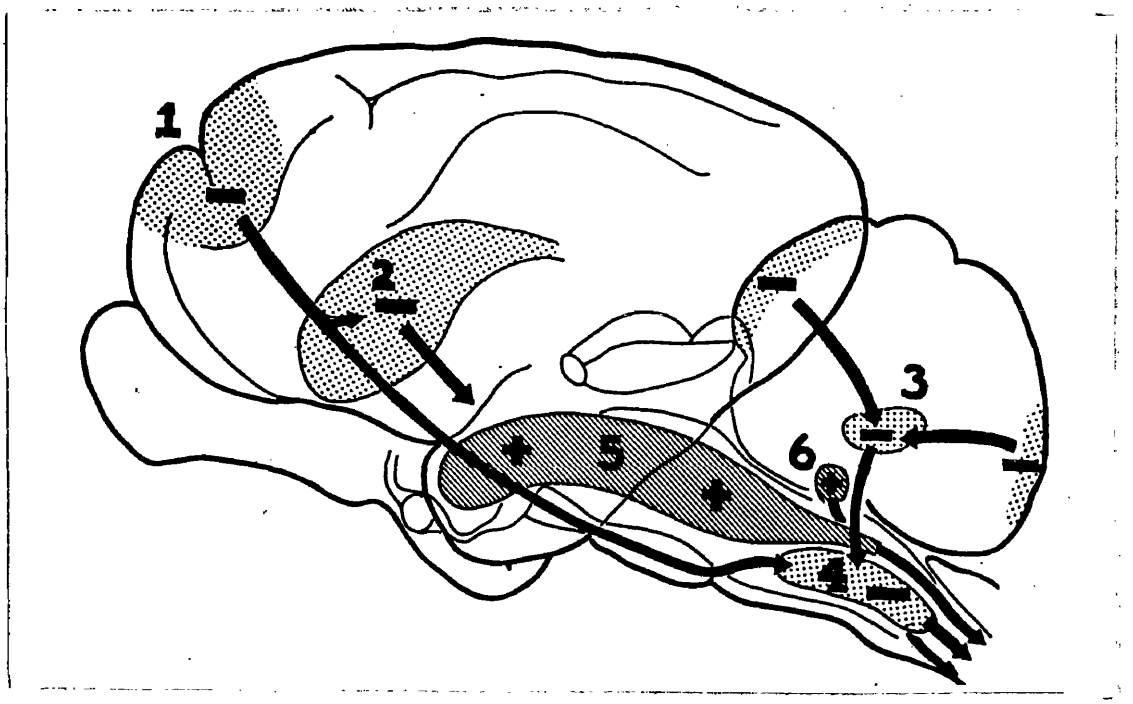


Fig. 6. Reconstruction of the cat's brain showing the suppressor and facilitatory systems concerned in spasticity.

Suppressor pathways are:- 1. cortico-bulbar; 2. caudato-spinal; 3. cerebello-reticular; 4. reticulo-spinal.

Facilitatory pathways are:- 5. reticulo-spinal; 6. vestibulo-spinal.

Reproduced from Lindsley, Schreiner and Magoun (1949.

optic thalamus. Its connection with the inhibitory bulbar reticular formation was demonstrated by McCulloch, Graf and Magoun (1946). Areas 4, 4S and 6 are therefore concerned with the maintenance of the tone of skeletal muscle.

In the mechanism for control of the tone of skeletal muscle the local reflex activity (employing the gamma efferent nerves, the intrafusal fibres of the muscle spindle, the spindle afferent nerves and finally the extrafusal fibres) is the final and the most important part. The circumstances in which use is made of either the alpha or gamma efferent route or various mixtures of the two are unknown. It is probable that for the maintenance of postural tone the gamma route is employed while for rapid movement with minimum reaction time the alpha route will be employed. Granit and his colleagues concluded that if this is the case there must be a mechanism for quickly adjusting the activity between one route and the other, thus varying the proportion of the two efferent systems in use.

Granit and Kaada (1952) studied the influence of stimulation of central nerve structures on muscle spindles in the cat. They found a highly efficient facilitatory mechanism for the muscle spindle in the brain stem and diencephalic reticular system. When this system is stimulated there is a slowly increasing acceleration of the spindle discharge. Less consistently, similar effects were obtained from the motor cortex, anterior lobe of the cerebellum and from the head of the caudate nucleus. Deceleration of spindle activity down to complete inhibition /

inhibition was obtained from bulbo-reticular inhibitory system and from the anterior lobe of the cerebellum in decerebrate rigidity. IB fibres from the Golgi tendon endings were not influenced by central stimulation. They concluded that the gamma efferent system is tonically activated from central regions.

Eldred, Granit and Merton (1953) found that in normal cats there is continuous gamma efferent activity affecting the spindles. This discharge is increased in decerebrate rigidity (Hunt, 1951). Granit, Holmgren and Merton (1955) using decerebrate cats showed that deceleration of spindle activity occurs when the anterior lobe of the cerebellum is cooled and that re-warming restores the spindle activity. They made the point that spindle paralysis produced by cerebellar ablation puts out of action the muscle length servo. Thus the muscle is deprived of the benefit of its own length measuring instruments. They suggest that the sign of dysmetria in human cerebellar diseases may be a manifestation of similar spindle paralysis. They finally concluded that it is likely that fixing the proportion of gamma and alpha efferent pathways in use in reflex movements is a function of the cerebellum.

PHYSIOLOGY OF TREMOR IN PARKINSONISM

James Parkinson was the first to separate the involuntary tremor of paralysis agitans from other forms of tremor.

Binet (1920) showed that tremor is present in normal people although /

although to a very mild degree and ordinarily is imperceptible. This tremor disappears only if the arm is well relaxed and in complete state of rest and on a resting plane. The tremor frequency in normal people is about 10 per second, which is the same as the rate of the alpha rhythm of the motor cortex. It was therefore thought that the tremor rhythm was due to the activity of the motor cortex (Area 4).

That the intactness of the pyramidal tract appears to be essential in the production of Parkinsonian tremor was suggested by the cases reported by Parkinson (1817), Wilson (1924) and Patrick and Levy (1922). In each instance, a Parkinsonian patient with marked tremor after developing a lesion of the pyramidal tract became free of his tremor although limbs were still rigid. Surgical section of the cerebral peduncle and the pyramidal tract has been shown to abolish Parkinsonian tremor either temporarily or permanently (Putnam, 1940; Bucy, 1940 and 1957; Oliver, 1949; Walker, 1952). Hammond, Merton and Sutton (1956) however doubted the view that the motor cortex was responsible for the tremor. They showed that under certain conditions the tremor rhythm disappears on closing the eyes - a state in which the alpha rhythm of the motor cortex is expected to increase. The rate of Parkinsonian tremor is between 3 - 6 per second while the alpha rhythm is 10 per second. Therefore, although the presence of the motor cortex (Area 4) with its tract appears to be essential, it cannot be the primary cause.

Meyers (1940) reported on 3 cases with Parkinsonian tremor who had most or all of the head of the caudate nucleus resected with marked improvement /

improvement, the tremor recurring only during emotional excitement. He was, however, convinced that the tremor was not initiated by impulses from the caudate nucleus. He considered that the caudate nucleus formed an indispensable part of the suprasegmental loop mediating such impulses. Electroencephalograms from prefrontal and premotor zones showed a slow rhythm of 4 per second coming in spindles that were synchronous with the exaggerated phase of clinical tremor whilst action potentials from the caudate nucleus showed no such electrical phenomenon.

Recently Hassler, Riechert, Mundinger, Umbach and Ganglberger (1960) studied the effect of stimulating the inner part of the globus pallidus and the oral ventral nucleus of the thalamus during 329 stereotaxic operations for extrapyramidal motor disturbances. They found that stimulation of the pallidum at frequency rates of 15 to 50 per second sometimes increased the tremor but at other times blocked it. Stimulation of the oral ventral nuclei of the thalamus had an even greater effect on tremor. It appears that the thalamus is probably of greater importance than the pallidum in the maintenance of tremor in Parkinsonism. This is in agreement with the fact that chemopallidectomy or electrocoagulation of the globus pallidus abolishes or greatly reduces tremor in about 45% of cases (Cooper et al, 1958; Spiegel, Wycis, Baird, 1958); whilst chemothalamectomy or electrocoagulation of the thalamus abolishes tremor in over 70% of cases (Cooper et al, 1958). In fact, Narabayashi, Okuma and Shikuba (1956) from /

from their experience on 26 cases with chemopallidectomy found that if tremor alone was present it rose to its pre-operative level at the end of two weeks but when tremor and rigidity were both present the degree of reduction of tremor depended upon the degree of reduction of rigidity. They also found that stimulation of the globus pallidus electrically did not increase the tremor unless the co-existent rigidity was increased. Spiegel and Wycis (1960) have suggested that the state of excitation of the pallidum depends largely on impulses it receives from the thalamus.

Excision of the premotor cortex was reported to relieve Parkinsonian tremor (Minckler and Klemme, 1943). The significance of this is difficult to assess but this area has been shown to be connected with subcortical nuclei and the reticular formation.

In recent years the reticular system and the brain stem have been shown to be of importance in the production of tremor at rest. Ward, McCulloch and Magoun (1948) have shown that tremor at rest resembling that of paralysis agitans in man can be produced in monkeys by lesions below the basal ganglia which destroy part of the mesencephalic and pontine tegmentum. Peterson, Magoun, McCulloch and Lindsley (1949) confirmed these findings and carried out some electromyographic (E.M.G.) studies on postural tremor in these monkeys with midbrain tegmental lesions. They found that in postural tremor there was regular alteration in agonists and antagonists at rates of 6 to 8 per second. Augmentation of the tremor occurred during passive stretch of an affected /

affected muscle and during its participation in postural adjustment. The tremor disappeared on active movement. A number of monkeys displayed action tremor and it was found that the common feature was the presence of lesions involving the superior cerebellar peduncle. E.M.G. studies of action tremor showed more dispersed bursts of action potentials without a clear cut alternation in agonists and antagonists.

Jenker and Ward (1953) studied the effect of stimulating various areas of the brain stem. They found that high frequency electrical stimulation of the medial reticular formation of the brain stem of monkeys produced rhythmical alternating peripheral movements analagous to tremor. They also found that the tremor was reduced or abolished by parenteral administration of anticholinergic drugs: the most effective one was scopolamine, and diethazine came second. They therefore advanced the hypothesis that Parkinsonian tremor is due to interruption of the rostral connections (from the basal ganglia and the cerebral cortex) to the medial reticular formation. They postulated that the de-afferented cells subsequently become hypersensitive to acetylcholine; that activation by locally liberated acetylcholine yields the observed tremor; and thus they explained why anticholinergic drugs abolished or reduced the tremor.

Folkerts and Spiegel (1953), although unable to identify a clearly defined tremogenic zone in the brain stem as claimed by Magoun and his associates, confirmed that electrical stimulation of the reticular substance resulted in tremor. They suggested that interruption of the /

the nigrofugal fibres was responsible for the production of tremor.

The role of the spinal cord and spinal reflex activity is not clear but it is certain that afferent impulses through the posterior spinal nerve roots are not of importance. Pollock and Davis (1930) showed that section of the dorsal spine nerve roots, while reducing rigidity and spasticity, has no effect on tremor. Mephenesin (Myanesin) a drug which acts on the internuncial neurons in the spinal cord has been shown by Stephen and Chandy (1947), Gammon and Churchill (1949) to abolish tremor and other hyperkinetic states when given intravenously. It is, however, possible that the principal action of mephenesin may also be in the brain stem because nystagmus was constantly observed as a side effect.

The physiology of skeletal muscle tone and tremor have been discussed in some detail because it is widely agreed that a proper understanding of the mechanisms involved is essential if progress is to be made in the pharmacology and therapeutics of Parkinsonism. This relationship will be discussed further in those parts of the Thesis which are devoted to reports of experimental work.

ENCEPHALITIS LETHARGICA

As this thesis is concerned with the clinical and pharmacological aspects of Parkinsonism following encephalitis lethargica, it is appropriate that the manifestations of encephalitis lethargica should be described, at least briefly. Excellent accounts on this subject have been given by Hall (1923), Boyd (1925), Main (1928, 1931), Economo (1931) and Wilson (1954) and the account given below is largely taken from them.

Historical:

Von Economo was the first to delineate and formulate this disease which he called Encephalitis Lethargica (Economo, 1917). Reference to epidemics which appeared on clinical grounds to be epidemics of encephalitis lethargica have been made by Crookshank (1922) and Economo (1931). These epidemics include:

(1) A serious epidemic in London between 1673 and 1675 described by Sydenham as "febris comatosa" because of the sleeping symptoms.

(2) Dubini's "electric chorea" (1846).

(3) "Nona" which occurred in Italy from 1890 to 1891.

Economo did not agree that the "Schlafsucht" of Tübingen (1712 to 1713) was probably an epidemic of encephalitis lethargica but thought it was probably one of influenza with pertusis. Hall (1923) made the point /

point that before the epidemic occurred in 1917 there had been a number of sporadic cases as far back as 1903.

As already stated, the first report of the epidemic was by Economo reporting from Vienna in 1917. This was followed by numerous reports from other parts of the continent (Cruchet, Montier and Calmette, 1917; Netter, 1918; Benard and Renaut, 1920) to mention only a few. From England came reports by Harris (1918), Hall (1918), Wilson (1918), Smith (1918), Buzzard and Greenfield (1919). The first report from Glasgow appears to be that of Findlay (1918), although Chalmers (1918) and Picken (1918) had earlier described cases in which the illness might have been attributable to encephalitis lethargica but which were said to be due to botulism or influenza. Other reports include those of Munro (1920) and Manson (1921); but about the most important record of the Glasgow epidemic was that of Main (1928 and 1931). Some of the patients described in her admirable thesis (Main, 1928) still survive, and further information about them is included in the present thesis.

Clinical Features of Encephalitis Lethargica

The clinical features were summarised by Economo as follows:-

> "The patients all showed a slight influenza-like prodromal condition with trifling pharyngeal symptoms, a slight rise of temperature which was soon followed by a variety of nervous symptoms, though generally one sign or another pointed to the midbrain as the source."
> "I noticed particularly in a few of these patients a condition /

condition of marked lethargy combined with disturbances of the eye muscles, recalling the mythical sleeping sickness "Nona" .....".

The clinical manifestations were divided into four types by Economo:

1. <u>The Somnolent-Ophthalmoplegic Form</u>.

The stage of somnolence is generally preceded by a prodromal stage which often comes on abruptly and lasts a few days. During this prodromal stage the patient complains of general discomfort, lassitude, headache, and occasionally vertigo and vomiting. Apart from a slight pharyngitis, catarrhal condition of the respiratory tract is rare. Signs of slight meningeal irritation may appear. The rise in temperature is slight but occasionally hyperpyrexia terminally may occur.

The somnolent stage appears within a few days of the prodromal stage and progresses. The patient falls asleep even when eating. In a large number of cases they can be aroused quickly but in some patients somnolence deepens into stupor and this is usually fatal. Ophthalmoplegia is seen commonly and nuclear paralysis is probably more common than peripheral paralysis. Third nerve palsy is the commonest and this is followed by sixth nerve palsy. Ptosis, weakness or paralysis of extrinsic ocular muscles, diplopia, nystagmus and pupillary changes are therefore frequently seen. The facial nerve is the next most common cranial nerve involved but others from the medulla oblongata may also be involved. Asthenia is usually severe and the muscles are frequently /

frequently hypotonic with loss of deep reflexes. Signs suggestive of cerebellar involvement are occasionally seen.

2. The hyperkinetic form.

Chorea and hemichorea may occasionally make their appearance in the somnolent type but in some patients this syndrome dominates the clinical picture. In some patients myoclonic jerks are more marked than choreiform movements.

The initial symptoms are more violent than in the previous type; prostration and failure of strength are more striking. Herpes labialis may be seen and sometimes it involves the whole face. Neuralgic pains, especially over the distribution of the trigeminal nerve but also in the limbs, are common. Boyd (1925) in the Winnipeg epidemic also noted this association between neuralgia and myoclonus. General mental unrest is commonly seen in this type. There is extreme restlessness, the patient talks incoherently, there is delirium with hallucinations (usually optical but sometimes tactical) and hypomanic behaviour may occur. Sleep reversal or inversion is usually seen in this type - the patient is awake at night and is drowsy during the day. Paresis of eye movements and pupillary abnormality are not as frequent as in the somnolent ophthalmoplegic type. Hiccough is common and may be due to myoclonic twitches of the diaphragm. In a considerable number of cases the hyperkinetic form is followed by the somnolent ophthalmoplegic type.

3. Amyostatic-Akinetic Form.

This /

This is the third most common form of presentation. There is a short prodromal stage as described for the two previous types and this is followed by a stage resembling Parkinsonism. The patient is weak and extremely slow and there is a fixed attitude reminiscent of catatonic stupor and passive attitudes are maintained as in catalepsy. The patient stares into space and looks demented, apathetic, resembling a case of dementia praecox. Excessive salivation, greasy skin and oedema of the legs are common. Difficulties in swallowing and speech may occur and paralysis of the soft palate has been observed. There may be some degree of insomnia with delirium and restlessness; some talk in their sleep and somnambulism may occur. A number of these patients recover completely but a considerable number progress to the chronic form of Parkinsonism.

4. Other methods of presentation.

Neuritic forms involving cranial or spinal nerves are seen and may occur alone during an epidemic. The trigeminal, the radial and ulnar nerves are the most commonly affected. The most common monosymptomatic form is singultus (hiccough). Hall (1923) stated that epidemics of febrile hiccough did not begin until late autumn of 1919, almost coincidentally with the hyperkinetic myoclonic variety. Boyd noticed a number of cases of hiccough in the second Winnipeg epidemic. Perhaps it should be mentioned that most of the patients who developed epidemic febrile hiccough did not suffer from the sequelae of encephalitis lethargica. Pseudotabetic and pseudoparetic forms sometimes occurred, /

occurred, and in the 1924 epidemic in Glasgow there were a number of cases with signs suggestive of disseminated sclerosis (Main, 1931).

Mental disturbances which occur during the acute phase of encephalitis lethargica include delirium, hypomaniacal states, perversion of conduct (seen amongst children), Korsakow psychosis, depression and catotonic stupor. Although excessive drowsiness is characteristic, in some epidemics delirium - usually of the occupational type - may be common: and these patients remain awake most of the night (inversion of sleep rhythm).

Sequelae of Encephalitis Lethargica

Main (1928) studied the sequelae of the 1923 Glasgow epidemic. She divided the results of encephalitis lethargica into five groups as follows:-

1. Complete Recovery - The patients regained their normal health and resumed their normal occupation, showing no residual signs of previous illness.
2. Incomplete Recovery - This group includes all patients with some defect but excluding Parkinsonism and perversion of conduction. The physical defects include: wasting of muscles and deformities. Other defects include mental retardation, mental instability and nervous instability (insomnia, drowsiness, irritability, tremor and headache).
3. Perversion of Conduct - This group is made up of children /

children having abnormal conduct such as violent conduct, theiving, sexual perversion and signs of moral imbecility.

4. Parkinsonism - The signs and symptoms will be described later in detail.

5. Died - Up to 50% have been quoted as the mortality rate but Wilson (1954) puts the average mortality rate at 35%.

It is to be noted that a patient may have either physical or mental disability or both. Thus a post-encephalitic patient may suffer from Parkinsonism and also have perversion of conduct or mental instability.

Parkinsonism

This is the commonest sequel and the most serious. Its onset may date from shortly after the acute stage (in fact the amyostatic-akinetic acute form resembles Parkinsonism); but the interval between the acute illness may be several years. In some cases of Parkinsonism there is no history of florid encephalitis lethargica, but such persons may well have suffered from the disease in an unrecognised or aborted form (forme fruste).

Clinical Features of Parkinsonism

Rigidity - this is the most common manifestation. Economo has described four types of rigidity, viz:-

1. Plastic type - The muscles display a well-marked tension at rest /

rest but passive movement does not cause any great increase in tone. There is however a tendency to assume or retain any posture imparted or spontaneously assumed by muscular action (flexibilitas cerea). This plastic rigidity leads to positive Head Dropping Test (Wartenberg, 1952) which is regarded as a useful sign in the diagnosis of difficult cases of Parkinsonism.

2. Proprio-reactive type - There is only a slight degree of tonicity at rest and no flexibilitas cerea but repeated passive movement causes an increase in the rigidity.

3. Reactive type - There is practically no tonicity at rest and no flexibilitas cerea. Passive movements provoke increase in the rigidity. Stimulation of the skin also produces the same result.

4. Reflectory type - Although active movement removes tension the slightest passive movements increase tension.

The rigidity in Parkinsonism is of the plastic variety unlike the clasp-knife type of 'pyramidal lesions'. Cogwheeling of the rigidity is however only seen when tremor is also present in the limbs. The present findings do not support Economo's statement that flexors and extensors are equally affected in Parkinsonian rigidity. His assertion is probably true when the rigidity is extreme. When the rigidity is only moderate one finds that resistance to passive movement is more marked in the flexors of the limbs than in the extensors. Another interesting fact about the rigidity of post-encephalitic Parkinsonism is its peculiar distribution; it may be unilateral or it may be /

be confined mainly to either the upper or lower limbs (more often the arms); it is usually more marked in the larger proximal muscles (muscles of the shoulder and hip joints) and becomes much less in muscles related to the small distal joints.

Other manifestations which are thought to be due to rigidity are the mask-like facies and lack of mimickry, slowness of movement, monotonous speech, muscular weakness and easy fatiguability. Wilson (1925) from his observations came to the conclusion that weakness of skeletal muscle is in inverse ratio of the muscle size. Thus the small muscles of facial expression and the small muscles of the larynx etc., used for speech show greater degrees of weakness than the larger muscles of the limbs. In a comparative study of the speech in Parkinsonism and in the normal he found that the time required in order to say a set of words was about the same in both groups but there was absence of flexibility (as measured by the number of vibrations per second) in Parkinsonism in contrast with the great variations in the frequency of vibrations in the normal. It is not quite certain whether the weakness is due exclusively to rigidity. Walshe (1924) showed that if the rigidity can be abolished by injecting dilute procaine at the motor points of the rigid muscles, that the muscle power improved and slowness of movement was abolished. Cruchet (1927) however showed that by injecting hyoscine parenterally he was able to abolish rigidity but not bradykinesia (slowness in executing movements). He therefore came to the same conclusion as Hall (1927) that bradykinesia /

bradykinesia was not dependent on impairment of muscular power. The problem of muscular weakness and easy fatiguability of the muscles will be further discussed in the main part of the thesis.

Gait

The gait in Parkinsonism is probably secondary to the rigidity and the flexed attitude of the patient. The gait is usually slow, shuffling and in small steps. Some patients, because of the flexed attitude, tend to hurry with small, short steps as if hurrying to try to catch up with the centre of gravity. This is the classic festinant gait of post-encephalitic Parkinsonism. In a few patients, festination is so marked that the patient is unable to walk in the ordinary way; he moves from place to place by short bursts of running. One patient in this present series shows this phenomenon - which has been described as 'kinesia paradoxa' (Brain, 1955). In some patients, a slight push applied to the chest causes them to walk backwards - usually at an increasing pace until they fall: this is the classic sign called retropulsion.

Deep reflexes.

The tendon jerks may be normal, exaggerated, diminished; and if rigidity is very marked it may be impossible to elicit any response. Harris (1927) however observed some abnormalities of the swing of the leg which was probably related to rigidity. Ekbom (1950) observed the phenomenon of "vario reflexia" in patients with an appreciable degree of tremor; the tendon jerk being sometimes elicitable and at other /

other times not elicitable depending on the phase of tremor when the stimulus was applied.

Tremor

The tremor of Parkinsonism is typically of the pill rolling variety with a rather slow frequency - about 3 to 6 per second. The tremor is at rest and characteristically stops when movement is being executed, returning when the movement is completed. Tremor is, however, not usually as prominent in post-encephalitic Parkinsonism as it is in other forms of Parkinsonism, especially paralysis agitans, rigidity being more marked in post-encephalitic Parkinsonism.

Tics

Tics are common in this condition and include convulsive yawning, hiccough, blepharospasm and recurring movements of mastication and swallowing.

Crises

There are two main types of crisis described in post-encephalitic Parkinsonism:-

1. The oculogyric crisis in which the eyes are strongly rolled or deviated upwards and to one side but rarely downward. Some authors also include paroxysms of fixed eye-staring as oculogyric crisis. The duration of crisis may be for only a few minutes but they may last for hours. It is said that oculogyric crisis may be the only indication that a patient has suffered from encephalitis lethargica and that if oculogyric crises are associated with Parkinsonism, then there is a strong /

strong presumptive evidence that the Parkinsonism must be post-encephalitic. This phenomenon has been studied in detail and will be described at greater length elsewhere in the thesis (Chapters II and III).

2. The respiratory crisis - One of the best studies of this type of crisis is that of Turner and Critchley (Turner and Critchley, 1925 and 1928). Other reports include those of Jelliffe (1926), Hess, (1927), Parker (1930), Hall (1923), Marie Binet and Levy (1922). Turner and Critchley classified the respiratory disorders of post-encephalitis into three groups, viz:-

(a) Disorders of respiratory rate - either tachypnoea or bradypnoea.

(b) Disorders of rhythm - either in the form of Cheyne-Stokes respiration, apnoeic pauses, and breath-holding attacks.

(c) Respiratory tics - include spasmodic cough, involuntary yawning, sniffing or hiccough.

Turner and Critchley noted that most of the cases observed in Britain up to 1928 were attributable to the 1924 epidemic. Disorders of rhythm and of rate are more important than respiratory tics. Breath-holding attacks may be ushered in by tachypnoea, and cyanosis may occur. Tetany may follow tachypnoea. Respiratory crises seem to disappear with time, and by 1929 the incidence of this complication was almost negligible (Jelliffe, 1929). This crisis, on account of its rarity, has not been studied in detail.

The Sweating Crisis

Another type of crisis, the sweating crisis, which has not been mentioned in the past except casually by Economo (1931) and by Narabayashi, Okuma and Shikuba (1956). This phenomenon has received special attention in the present thesis and is discussed fully in Chapters II and III.

Deformities

The subject of deformities in Parkinsonism has not received much attention in the past. The flexed attitude and probably the "main d'accoucher" deformity of the hands are the only types of deformity written about - even in monographs dealing with Parkinsonism. The deformities seen in the group of patients surveyed in this thesis have been studied in some detail (Chapter V).

Neurosympathetic and neuroglandular derangements

These include sialorrhoea which is generally more marked in post-encephalitic Parkinsonism than in paralysis agitans; greasy skin from excessive activity of the sebaceous glands, vasomotor disturbances such as coldness of the extremities, acrocyanosis and local oedema. Other manifestations are those affecting the ductless glands and include diabetes insipidus, dystrophia adiposo-genitalis, and more rarely glycosuria.

Psychic state

In post-encephalitic Parkinsonism depression is probably the most common psychic distrubance, but it is surprising that the incidence of depression /

depression is not higher in patients suffering from post-encephalitic Parkinsonism. Other manifestations of mental disturbance include paranoid psychosis, hallucinations and agitated melancholia. Perversion of conduct was seen in the young but it seems that when they reach adult age they become less anti-social and develop fairly normal behaviour. There does not seem to be much intellectual impairment as would appear to be the case on casual observation of the patients. A comprehensive study of the mental sequelae of chronic encephalitis lethargica has been made by Cooper (1936).

Treatment of Parkinsonism

James Parkinson, influenced perhaps by the practice of blood letting which was fashionable at the time when he wrote his classic essay on the Shaking Palsy, suggested that in attempting to effect a cure, blood should be taken from the upper part of the neck and that vesicants should be applied to the same area. Thereafter the "Sabine" liniment was to be applied at the site of venesection in order to produce a purulent discharge. If the volume of discharge was found to be insufficient, fresh blisters were to be produced and the liniment re-applied. He was opposed to the giving of medicines internally; and he also declared that as the muscular weakness was not due to constitutional debility, no benefit could be expected from tonics or a highly nutritious diet.

A /

A similar form of treatment was suggested by Netter (quoted by Economo, 1931), in the acute stage of encephalitis lethargica. An abscess is formed by injecting 1 ml. of pure old turpentine oil into the deepest layer of the skin on the lateral aspect of the thigh. Between the sixth and eighth day the abscess is incised and the pus allowed to escape. The aseptic pus was stated to contain antigens of the pathogenic virus - a claim which does nothing to inspire confidence in the therapeutic value of the regimen.

As regards the chronic post-encephalitic disease, the use of intravenous iodine alone or in combination with other adjuvant therapy was said to be the best form of therapy for the disease process (Economo, 1931). The iodine was either in the form of "Pregl's Iodine" or a 10% solution of sodium iodide if Pregl's Iodine was not available. Precise instructions are set out in the literature regarding the volume of this solution recommended for intravenous injection, but the treatment is obsolete. Pyrogens (malaria therapy) also had their vogue and were likewise abandoned.

Other adjuvant treatment include the use of mercury immunotions, intensive course of arsenicals, grafting of the parathyroids from calves or administration of parathormone intravenously three times daily for two to three months. X-ray irradiation of the head was also carried out for some time. It was supposed to cause hyperaemia of the atropic basal ganglia, thereby in due course restoring the function of the basal ganglia to normal. There was no proof that these methods of treatment /

treatment had any value and they were given up. In retrospect they are chiefly of interest in adding to the voluminous literature which reveals the remarkable credulity of patients and physicians alike.

Symptomatic Treatment

There were, however, other drugs of undoubted value used in the relief of symptoms. Until about 1945 preparations derived from the solanaceous plants (Atropa - belladonna, Hyoscyamus niger and Datura stramonium) were widely used in the symptomatic relief of Parkinsonism. Charcot is said to have introduced their use in Parkinsonism about 1874 (Goodman and Gilman, 1958): they were prescribed as the tinctures and dried extracts of belladonna, stramonium and hyoscyamus and also the pure alkaloids were used - atropine and later hyoscine. The "Bulgarian belladonna Treatment" introduced by Ivan Raeff in 1926 was very popular for a time, but there was some controversy as to the relative merits of the Bulgarian belladonna and the English belladonna (Alcock and Carmichael, 1938; Neuwahl and Fenwick, 1937; Hill, 1938). Vollmer (1940) however showed that the effect of the Bulgarian treatment was due to the contained belladonna alkaloids and not to the dietetic regimen in this form of treatment or to any other special substance contained in the Bulgarian belladonna. The alkaloids - hyoscine and atropine (or alkaloidal salts) - have been used in preference to galenicals (extracts, mixtures and tinctures). Hyoscine and /

and atropine can be given orally either in the form of a mixture or in the form of pills. Suitable alkaloidal preparations can also be given by subcutaneous injections, and it appears that better results are obtained from parenteral administration.

In post-encephalitic Parkinsonism large doses of the belladonna alkaloids are often required (Hall, 1937). Even in moderate doses, however, side-effects are common, and these include excessive dryness of the mouth and throat, paralysis of accommodation for near vision, intractable constipation, delirium, hallucinations and hyperthermia.

The slow-acting galenicals (dry extracts) have been used with limited success to produce sustained therapeutic effects. The main requirement however was a drug which would be more selective than those of the atropine group - counteracting the main disabilities of Parkinsonism but lacking unpleasant side-effects. New synthetic drugs were produced which relieved rigidity and tremor (probably by a central anticholinergic effect), but which had minimal anti-muscarinic action on the post-ganglionic fibres of the parasympathetic nervous system. The most important of these new drugs are:-

1. Benzhexol (Artane). The clinical usefulness of this drug was first reported by Corbin (1949) who found that it was effective in 71% of post-encephalitics; Doshay and Constable (1949) who obtained good results in 76% of post-encephalitics. Other reports include those of Schwab and Tillman (1949) and Berkowitz and Alverman (1952). The last of these authors however found no difference between the effects of benzhexol and those of stramonium.

Although /

Although Cunningham et al (1949) found that in experimental animals atropine sulphate is twice as strong as benzhexol judged by its spasmolytic effect on isolated intestine, and eight and three times as strong as an antisialogogue and as a mydriatic respectively, side-effects such as dryness of the mouth and blurred vision were still complained of in the conventional doses needed for the relief of rigidity and tremor. Further, mental symptoms (severe confusion, attempted suicide, paranoid psychosis, hallucinations and excitement) were reported. 10 out of 52 patients in the series reported by Porteous and Ross (1956) had mental symptoms as a side-effect. Fortunately the incidence is generally very much lower than this.

2. Caramiphen (Parpanit). The results of clinical trials with this drug were reported by Dunham and Edwards (1948) and Schwab and Leigh (1949). This drug appears to have no advantage over the solanaceous drugs except that side-effects may be less. The drug is, however, not well tolerated by patients suffering from arteriosclerotic Parkinsonism.

3. Diphenhydramine (Benadryl). The antihistaminics were also tried and diphenhydramine was found to be about the most effective. However, by the oral route its effect on rigidity and tremor are mild, and drowsiness (a side-effect seen in up to 50% of cases) was a serious drawback in the majority of cases; but in patients complaining of insomnia this side-effect was beneficial. The earliest report on the clinical effects of diphenhydramine on Parkinsonism include those of

McGavalli /

McGavack, Elias and Boyd, (1947); Budnitz (1948) and Ryan and Wood (1949).

4. Ethopropazine and Diethazine. Both drugs are close homologues and are related chemically to the phenothiazine group of drugs. Diethazine (diparcol) was first employed for the symptomatic relief of Parkinsonism in 1946 (Sigwald and his colleagues, 1947). However, its use was soon abandoned because of its toxic effects, especially those on haemopoietic tissue leading to leucopenia and agranulocytosis, and an action on the kidneys giving rise to albuminuria. Furthermore, most patients were unable to tolerate adequate therapeutic doses owing to side-effects such as drowsiness, vertigo, hyperthermia and temporary paralysis. Ethopropazine (Lysivane, parsidol) was found to be more easily tolerated with less side-effects and with a much smaller incidence of leucopenia and agranulocytosis. Reports on its clinical usefulness include those of Garai (1951), Gillhespy (1953), Doshay, Constable and Agate (1956).

5. Curare and Mephenesin. Curare was first used about 1927 (Wilson, 1954) but was abandoned because of the dangerous skeletal muscular paralysis it sometimes produced. Furthermore it had to be given by injection many times daily. Recently, however, Berger (1956) reported on the great advantage of using repository curare given intramuscularly in combination with the standard anti-Parkinsonism drugs such as benzhexol. This report has been received without much enthusiasm. Mephenesin (Myanesin) was tried for a time but has been largely /

largely abandoned because of its rather poor effect when given orally and because large doses are required. Reports on its use include those by Stephen and Chandy (1947); Berger and Schwartz (1948) and Gammon and Churchill (1949).

6. Orphenadrine (Disipal). This is very closely related to diphenhydramine and is being used increasingly in Parkinsonism. Reports on its clinical value include those of Gillhespy and Ratcliffe (1955), Doshay and Constable (1957), Rosenfield and his colleagues (1959). The therapeutic effects of this drug will be described in detail in a later section of the thesis.

Other drugs of less importance which have been used include the following:-

1. Procyclidine hydrochloride (Kemadrin).
   (Schwab and Chafetz, 1955; Zier and Doshay, 1957).
2. Bentropine sulphonate (Cogentin). (Doshay, 1956).
3. The Glutarimides (Ciba 10870). (Hughes, Keevil and Gibbs, 1958; Balestrieri and Signorato, 1958).
4. Testosterone and heparin (Weinberg, 1954).
5. Xoxazolamine ("Flexin"). (Rodriguez-Gomez et al, 1956; Amols, 1956).
6. Oral Hypoglycaemic agents - Tolbutamide and Chlorpropamide (Gates and Hyman, 1960; Gillhespy and Paton, 1960; Robertson, 1961).
7. Tigloidine. (Trautner and Noak, 1951; O'Rourke et al, 1960). /

This substance is related to atropine and is an ester of pseudotropine - an alcohol, and tiglic acid. It is of some value in Parkinsonism and in paraplegic patients.

Recent reviews on the drug treatment of Parkinsonism include those of Doshay and Constable (1951); Garland (1952); Miller (1953); Ebauch and Drake (1954); Critchley (1958). Many other drugs are used occasionally to give symptomatic relief. These include phenobarbitone, amphetamine, bulbocarpine, new antidepressive drugs for very depressed patients, and various preparations for the management of constipation - often a troublesome problem in these patients.

This thesis is mainly devoted to describing methods of assessment of drug therapy in Parkinsonism (a subject which continues to arouse considerable controversy) and the mode of action of drugs used in the symptomatic relief of rigidity and tremor in this disease. Most attention has been given to the pharmacological actions of orphenadrine on skeletal muscle. This work has emphasised the need to intensify the study of drugs which act directly on the peripheral servo mechanism - the final stage in the series of events leading to changes in the tone of skeletal muscle.

CHAPTER II

CRISES IN POST-ENCEPHALITIC PARKINSONISM

In Chapter I (General Introduction) it was mentioned that two types of crisis have been described in post-encephalitic Parkinsonism, namely the oculogyric crisis and the respiratory crisis. In this section of the thesis it is proposed to report on the crises which have been observed in the present series of patients. As the oculogyric crisis is more prevalent and causes great distress, much time has been spent on the study of its various aspects and most of the discussion will therefore be devoted to this form of crisis.

In individual cases of post-encephalitic Parkinsonism the disability and distress caused by crises may in fact be much greater than that resulting from tremor and rigidity. Some patients with minimal tremor and rigidity experience severe crises lasting for 12 hours or more and these sometimes occur as often as three times a week. A general practitioner who suffered from post-encephalitic Parkinsonism, writing on his disabilities (Lancet, 1948), regarded sialorrhoea as his greatest tribulation - in spite of the fact that he had very marked rigidity and was able to type with only one finger.

Historical

J. P. Albreit was probably the first writer on this subject to report on a case of oculogyric crisis. In 1695 he reported the case of /

of a girl of 20 who had typical symptoms of encephalitis lethargica and who subsequently developed episodic upward rolling of the eyes.

Most of the early writings on oculogyric crises occurring as a sequel to this pandemic of encephalitis lethargica came from Western Europe (Levy, 1922; Fischer, 1924; and Meyer, 1924). Cases of oculogyric crises were not reported from North America until 1925 (Hohman, 1925); reports from this country appeared much later. Duncan (1924), in a comprehensive account of the sequelae to encephalitis lethargica made no reference to crises. From 1926 however a number of reports appeared (Barkas, 1926; Bramwell, 1928; McCowan and Cook, 1928; Williamson-Noble, 1928; Hall, 1931).

Incidence

A total of 67 patients were studied. They have been cared for at Stobhill General Hospital, Glasgow, for periods varying from 4 to 30 years. Many of them had suffered from encephalitis lethargica during the epidemic that followed the First World War. There are 32 men and 35 women. In 27 of them (10 men and 17 women) crises punctuate the course of the disease; a patient may have more than one type of crisis. Clinically three types of crisis have been observed in this series of patients suffering from post-encephalitic Parkinsonism; first, the classic oculogyric crisis which was seen in 20 patients. A second type, the respiratory crisis, was seen in only one patient. A third type, in which various manifestations of disturbances in the autonomic nervous system - particularly sweating - are the main features, was also observed in 8 patients. Table 1 gives the /

TYPE OF CRISES.	NO. OF MALES.	% OF TOTAL NO. OF MALE PATIENTS.	NO. OF FEMALES.	% OF TOTAL NO. OF FEMALE PATIENTS.	% FOR BOTH SEXES COMBINED.
OCULOGYRIC	6	20%	I4	40%	29.8%
SWEATING	5	I5.9%	3	8.5%	II.9%
RESPIRATORY OR BREATH-HOLDING ATTACKS	-	-	I	2.8%	I.5%

Table 1. Frequency of various types of crises in post-encephalitic Parkinsonism.

the frequency of these three types of crisis. The incidence of oculogyric crisis in this series (29.8%) is rather high when it is compared with 15.6% in Hall's series of 384 patients and 17% of 136 patients reported by McCowan and Cook. The higher incidence of oculogyric crisis in the present series is probably due to the fact that a number of these patients were admitted because of the severity of their oculogyric crisis, and in this sense an element of selection must be noted: this may or may not apply to other workers' series.

Clinical features

Personal observations were carried out at all stages of these crises. Various phenomena were noted systematically: ocular deviation, the size and reaction of the pupils, severity of tremor and rigidity, sialorrhoea, blood pressure, heart rate, the occurrence of flushing of the face and conjunctiva, sweating and the amount of noise (e.g. moaning, howling, weeping, or general noisiness) made by the patient.

OCULOGYRIC CRISIS

The 20 patients affected have had oculogyric crises of all degrees of severity and occurring at intervals varying from a few days to several months. The most severe form of oculogyric crisis occur much more frequently in women than in men. There is also a higher incidence and frequency of crises in general among women patients. Again the individual patient may have crises which are sometimes severe and sometimes /

sometimes only mild.

Prodromal stage

Nurses who have had long experience in the care of post-encephalitics can often foretell the onset of an oculogyric crisis. The patient who has been ambulant feels less inclined to leave his bed; or if he is up he is slower in his movements and gait. At this stage the conjunctivae may be a little injected.

Emotional changes are common. Some patients become more quarrelsome for a day or two before a crisis. Others are depressed for some hours before the crisis. Some experience an aura before the crisis develops: the sensation is evidently unpleasant and even fearful, but descriptions are vague. One patient breaks out with repetitive and apparently meaningless jargon shortly before the actual rotation of the eyes. All have a preoccupied staring expression just before the ocular movements occur. Nystagmoid movements may be observed at this point; and in a few patients the appearance of the eyes and a state of fear combine to produce a facial expression of terror.

The stage of tonic deviation or rotation of the eyes.

The eyes are usually rotated directly upwards but sometimes upwards and laterally, and in two patients in this series the eyes are sometimes rotated downwards. The direction of rotation is nearly always constant for each patient, but on occasion upward rotation alone is present in a patient who usually has upward and lateral movement. /

movement. It is of interest to note that when lateral movement of the eyes is present, the eyes are usually directed away from the side of the body showing the greater degree of muscular rigidity. Skew movements of the eyes have been observed in one patient during some attacks. In a few patients the direction of rotation of the eyes varies even in the same episode. The eyes are usually open and the patient has a fixed stare. Three patients however suffer from photophobia and this causes them to keep the eyes tightly closed. They tend to lie on one side and try to pull the bed-clothes over their eyes. Two patients occasionally experience drooping of the eye-lids and cannot voluntarily open the eyes.

In the fully established oculogyric crisis the eyes are fixed. Just before this stage is reached, a well-marked vertical nystagmus with the quick component movement upwards is often observed. There is usually an associated flickering movement of the upper eye-lids.

At the fully established stage voluntary horizontal conjugate movement of the eyes is either impossible or, if it can be executed, is only momentary. Voluntary movement of the eyes downwards is usually impossible. If a patient has been persuaded to move the eyes into the horizontal or downward position, it is characteristic that upward conjugate deviation is restored by a very sudden movement of the eyeballs. Congestion of the scleral conjunctiva is also obvious during an oculogyric crisis. In the fully developed case engorgement of the vessels may be extreme: sometimes a large number of dilated capillary vessels are visible in either the lateral or medial limbus or both (Figs. 7

and /

(a) (b)

Fig. 7a. Severe oculogyric crisis in woman aged 56 years; flushed face, suffused conjunctivae, and frothing at mouth. Blood pressure rose to 204/110 : heart rate 96.

Fig. 7b. Same patient as 7a when not in crisis. Blood pressure 160/90 : heart rate 72.

(a) (b)

Fig. 8a. Mild oculogyric crisis in man aged 42 years. Flushed face but no significant rise in blood pressure or heart rate.

Fig. 8b. Same patient, when not in crisis.

and 8). In most cases of severe crisis excessive lachrymation is obvious, and there is then occasional escape of tears from the eyelids.

During an oculogyric crisis the pupils are usually dilated, although fixed small pupils have been noted in one patient. Reaction to light is characteristically sluggish. As convergence is rarely possible, reaction to accommodation can rarely be determined satisfactorily.

During a severe crisis, facial flushing is always present and slight congestion of the skin may occur as part of the prodromal syndrome. The head is tilted so that usually the occiput and the eyeballs move in the same clockwise direction. Sometimes there is also head retraction. The skin of the forehead may or may not be wrinkled. Muscular rigidity is often increased. Tremor may become more marked; but patients with slight tremor may lose it altogether during oculogyric crisis - perhaps because the movements are eliminated by the state of increased muscle tonus. A remarkable phenomenon is the obvious unwillingness to move (bradykinesia) and sometimes immobility is absolute (akinesia). The patient abandons the struggle to move his limbs; the whole body is extremely rigid and he has to be moved like a tailor's dummy. When they are in the throes of an oculogyric crisis the majority of patients are unable to feed themselves; but if food is put into the mouth patients show little difficulty with mastication or deglutition.

Vertigo /

Vertigo, objective or subjective in type, is complained of by 8 out of 20 patients during crises. Headache - usually frontal, but rarely occipital - is a common complaint but it is not incapacitating. Increased salivation is seen in less than one half of the patients and in these it is inconstant. The blood pressure may be raised by as much as 60 mm.Hg. systolic and 30 mm.Hg. diastolic; tachycardia is common and is not constantly related to change in blood pressure. Irregular respiration is seen in a few patients; tachypnoea is followed by variable periods of apnoea.

Emotional disturbances occur in all severe cases. Despite rigidity and immobility during the crisis, these patients are rarely silent: grunting, mumbling, moaning or howling are commonplace; and some emit sudden squawking sounds - which one resident medical officer described as being like the plaintive cry of a seagull. The noise is sometimes loud enough to be audible more than 200 yards away. The patients cannot explain why they shout or moan. Three patients are invariably quiet during crises, and it is noteworthy that in these patients flushing of the face is trifling or absent altogether. Some patients repeat particular words or sentences - but these convey little or nothing to the observer. The patients describe their feelings as being "terrible", and it is evident that they are in a state of fear. During a crisis one patient sometimes has outbursts of uncontrollable laughter. Hallucinations have never been detected. Incontinence of urine was seen occasionally during oculogyric crisis.

SWEATING CRISES

The post-encephalitics in this series have revealed intolerance for warmth as compared with normal people. They tend to sweat much more easily and prefer the cold weather to hot weather.

Eight patients have paroxysmal attacks of excessive sweating even in the winter months. The phenomenon is so sharply defined and so completely independent of environment, that it has been designated a 'sweating crisis'. Five of these patients are men and three are women (see Table I). Four of them have severe attacks periodically. Two patients (one man and one woman) display both oculogyric and sweating crises; and these two types of crisis may occur simultaneously or at different times.

The crisis can occur at any time but are much more frequent late at night or early in the day. During the crisis severe tremor is commonly present but it is thought that only occasionally is the increased muscular activity an important factor accounting for sweating. Sweating is so profuse that it may necessitate a change of garments and bed clothes every hour - or even more frequently; and this has occurred in the absence of any marked increase in the degree of tremor beyond that normally present. Further, in one patient where oculogyric crises are associated with the development of severe tremor, sweating is not excessive. In a sweating crisis there is usually flushing of the face and sometimes congestion of the conjunctiva. The skin of the limbs may also be hyperaemic. The axillary temperature may exceed 100° F.

One patient whose tongue normally shows marked tremor, makes clicking noises during a sweating crisis by alternately protruding and partially withdrawing the tongue. Severe cyanosis has been seen in this patient during sweating crises. This is attributed to mechanical obstruction: there is marked forward flexion of the neck and because the tongue is often extruded, breathing through the mouth is made more difficult. Increased oxygen utilisation from excessive tremor may also be a minor contributory factor.

There is severe tachycardia during a sweating crisis: the heart rate may reach 150/min. The cardiac rhythm is usually regular but very rarely extrasystoles occur. The systolic blood pressure rises by 20 - 50 mm.Hg. and the diastolic pressure by about 20 mm.Hg. Excessive salivation is sometimes present.

RESPIRATORY CRISES

Only one patient suffers from this form of crisis. Because of the rarity and the rather transient nature of this form of crisis only a limited amount of information can be offered. This patient, a woman, suffers from what may be termed "breath-holding attacks". This is usually preceded by a period of motor excitement during which the arms and head manifest marked coarse tremor. After about five to ten minutes this is followed by the period of apnoea during which she may be either cyanosed or pale. She appears to be in a trance during the period of apnoea as she is scarcely accessible to questions. Surprisingly /

Surprisingly enough, these spells of apnoea can be aborted by shaking the patient vigorously by the shoulders, as if to rouse her from deep sleep.

ILLUSTRATIVE CASES

Case 1. J. Pat. Woman, aged 56 years. This patient was admitted in 1946. No history of a febrile illness resembling encephalitis lethargica could be elicited. She had gon to Australia in 1926 and two years later, following a tonsillectomy, she found that she had muscular weakness on one side of the body and tremor on the other. She returned to the United Kingdom and was eventually admitted to Stobhill General Hospital. Oculogyric crises began in 1942.

On examination at the time of admission she was described as a thin woman with mask-like facies. She had typical Parkinsonism tremor affecting the limbs, head, tongue and eyelids. There was some loss of muscular power with wasting. Speech was monotonous. She seemed to be of average intelligence and had a fairly good memory. Deep reflexes were normal; plantar responses were flexor. Examination of other systems revealed no abnormality except systolic hypertension, B.P. 170/86.

Examination in 1959 confirmed the former findings. There was moderate hypertonicity of all limbs, more marked in the left arm. Muscle power in the right arm was fairly good but was diminished in other limbs. The pupils were small, reacting to light but not to accommodation; /

accommodation; there was slight weakness of the right lateral rectus muscle. Blood pressure 170/90 mm.Hg.; pulse rate 80/min.

Treatment. In 1950 she had been given benzhexol 20 mg. daily, but in 1953 it was withdrawn owing to unbearable side-effects and she started to receive Tincture of Stramonium 2 ml. daily.

Comment on present condition (1960). She suffers from very severe oculogyric crises which, in the absence of any treatment, may last up to 24 hours. She shouts during the crises. The face is flushed and cunjunctiva injected, and there is some lachrymation. Excess salivation is invariably present. Tremor and rigidity are increased. On a few occasions she sweats but she does not have severe sweating crisis. The blood pressure is usually increased (the systolic pressure rising by about 10 to 40 mm.Hg. and the diastolic pressure by 10 to 30 mm.Hg.); the systolic pressure exceeds 200 mm.Hg. and on some of these occasions she has had attacks of mild epistaxis. The heart rate rises by about 10 to 20 beats per minute. In some attacks there is vertigo with a tendency to fall to one side (if patient is sitting up). It is evident that often she develops an oculogyric crisis on the days she expects her sister to pay a visit. The crisis usually starts a few hours before the visiting hour.

Case 2. M. Cra. Woman aged 40 years, admitted in 1944. She gave a history of having had "sleeping sickness" at the age of 7. Some years later she developed stiffness in both lower limbs with some difficulty /

difficulty in walking.

On examination at the time of admission she was found to be well nourished but not very intelligent. She had increased muscle tone and tremor in all limbs. The pupils were equal and of normal size, reacting to light and accommodation. The tendon reflexes were exaggerated. Examination of other systems revealed no abnormality. Oculogyric crisis was first noted in June 1949, about 22 years after the attack of encephalitis lethargica.

Examination in 1959 showed no deterioration. Rigidity and tremor were, however, almost entirely confined to the left side. The pupils were normal in size and shape, and reacted to light and accommodation. She had a festinant gait. Speech was slow and monotonous. The reflexes were normal apart from moderate increase in the knee jerks. The blood pressure was 130/90; pulse rate 90-100/min.

Treatment. She had been treated originally with Tincture of Stramonium (2 ml. daily), but in October 1950 she received instead benzhexol (Artane) 30 mg. in divided doses.

Comment. This patient has frequent oculogyric crises, up to three per week. If treatment is inadequate they may last for 6 - 12 hours. They may be precipitated by emotional upset or by annoyance (e.g., prunes for breakfast). It would appear that this patient can sometimes bring on oculogyric crises at will.

During the crisis the eyes are rotated upwards and to the right. Pupils dilate but react only sluggishly to light but not at all to accommodation. /

accommodation. The usual vaso-congestion is present. Salivation is not excessive but lachrymation occurs. She looks demented and is often noisy. During a crisis respiration is irregular: following periods of apnoea the breathing is rapid and shallow.

The blood pressure does not rise significantly. The greatest rise in the systolic and diastolic pressures is 10 mm.Hg. and 5 mm.Hg. respectively. The pulse rate may rise up to 20 beats per minute.

Case 3. J. McM. This man, aged 50 years, was first admitted to Stobhill General Hospital in 1933, following a "fit" in the street. The history was obtained from his wife. At the age of 14 (about 1924) the patient "suffered from sleeping sickness", and received treatment in hospital. Subsequently he appears to have been completely free from symptoms for 7 years: the post-encephalitic syndrome began in 1933 - about $2\frac{1}{2}$ years before his first admission to Stobhill General Hospital. He complained of tremor affecting the right side. The disability was progressive: dysarthria developed and hypersalivation became troublesome.

The clinical notes at the time of admission refer to a marked tremor affecting the left arm and leg. The pupils were then irregular and did not react to light or accommodation. He was sweating excessively.

He was discharged in 1934 but was re-admitted shortly afterwards. At this time it was noted that he had an expressionless face and marked tremor of all limbs, but the face and tongue were not involved. He was /

was again noted to be sweating profusely. Reflexes were normal. Examination of other systems showed no abnormality.

Examination in 1959 showed deterioration. He was now bedridden with flexion deformity at both knees. Tremor was present in all limbs, and also in the lips, jaw and tongue. Ptyalism was still present. He was unable to feed himself and had some difficulty in swallowing. His speech was very indistinct. Muscle tone was moderately increased, especially on the left side; muscle power was generally poor. There was dissociation of eye movement although there was no definite palsy of extrinsic ocular muscles. His blood pressure was 110/70 mm.Hg. and the pulse rate 72-80/min.

Treatment. From 1942-1950 he was treated with a strammonium and hyoscine mixture. Benzhexol was substituted in 1950 and a marked improvement in his condition was noted. Tremor and sweating diminished, muscle tone became normal, and he had a feeling of well-being. Later that year his treatment was suddenly changed to caramiphen hydrochloride (Parpanit) and deterioration followed within a week. Benzhexol was restarted in a dosage of 15 mg. daily and he has remained on this ever since.

Comment. Despite receiving benzhexol 15 mg. daily, sweating crises are frequent. Some are very severe, requiring a change of garments and bedclothes three times in one hour. He does not have oculogyric crises. The rise in systolic and diastolic pressures during severe attacks is up to 50 mm.Hg. and 20 mm.Hg. respectively.

The /

The degree of tachycardia also varies, but on one occasion the cardiac rate was over 150 per minute. Commonly the cardiac rate is between 120-136 per minute.

Case 4. W. Sha. This man aged 54 years, was first admitted to Stobhill General Hospital in August 1927. He gave a history of an "influenzal" illness six years previously. Three years after the attack of influenza he began to have tremor in his right hand and shortly afterwards in his right leg.

On examination at the time of admission he was found to have no difficulty in walking. There was increased muscle tone which was more marked in the legs. He had typical Parkinsonian tremor and facies. Both pupils reacted to light and accommodation. The deep reflexes were normal and the plantar responses were flexor. No abnormality was found in the other systems.

Oculogyric crises associated with fever and sweating began in 1938, 17 years after the acute phase of encephalitis lethargica. By 1959 his condition showed no material change, though judging by the medical records, tremor and rigidity seemed to have increased slightly. His blood pressure was 130/80 and he was not subject to tachycardia.

Comment. Both types of crisis (oculogyric and sweating) occur in this patient and they may be present simultaneously. More commonly however during sweating crises, involvement of the eyes is restricted to staring without tonic deviation or rotation. The effect of emotion in precipitating oculogyric crises is seen in this patient: they /

they often occur a few hours after he has been beaten in a game of billiards or when he has lost a substantial bet. However, curiously enough, after being told of the death of his father, 36 hours elapsed before a crisis occurred. In this patient the blood pressure during a crisis is much less than in Case 3: the increase does not exceed 30 mm.Hg. systolic and 10 mm.Hg. diastolic. Tachycardia is also much less, the maximum rate observed being 120 per minute.

Case 5. C. McM. A woman aged 56 years. She was admitted to Stobhill General Hospital in December 1948. She had been well until the age of 24 (1928) when she developed "sleepy sickness": she was treated at home. Shortly after the acute phase, she noticed tremor of the left hand, and later of the right hand. Six years after the acute phase of encephalitis lethargica she began to have oculogyric crises. These episodes occurred about twice a week and lasted some 24 hours. During a crisis she felt as if she were going to fall, or that objects in the room were rotating round her. She continually had double vision with one image above the other, but during an oculogyric crisis diplopia was much worse. She managed to do her housework until four years before her admission to hospital.

On examination at the time of admission (1948) she was reported to be a well built woman with tremor of the hands and tongue. She had a sluggish speech and moderate deformity of the limbs. The pupils were normal in size and reacted to light and accommodation.

The /

The deep reflexes were normal and the plantar responses were flexor. The other systems showed no abnormality.

Examination in 1959 confirmed the findings of 1948 but the rigidity was mainly left-sided. The tendon reflexes were exaggerated but the plantar reflexes were flexor. The blood pressure was 160/90; pulse rate 70/min.

Treatment. She has been receiving benzhexol 20 mg. daily since 1953.

Comment. Her crises are not now as frequent as they were, but their severity has not diminished. During a crisis she repeats endlessly a meaningless formula of words. The eyelids may droop and she is unable to open her eyes voluntarily (she raises the upper lid with her fingers). Superficial vasodilatation is very obvious: large numbers of distended capillaries are visible in the scleral conjunctiva. She is not noisy (no shouting) but is often very weepy. The blood pressure during crisis may rise and is sometimes as high as 204/110; and the cardiac rate may increase to 120/min.

Case 6. J. Cam. Male, aged 57 years. This man had an influenzal illness in 1917 lasting one month and during which he was very drowsy.

He has been in Stobhill General Hospital since 1943, although he was in the hospital for short periods in 1933, 1934 and 1941.

Examination at the time of admission showed that he had slight weakness of the right side of the face and a mask-like expression.

He /

He had no loss of muscle power and the reflexes were normal.

Examination in 1959 showed deterioration. He had a moderate degree of rigidity of his limbs, more marked on his left side. His muscle power was rather weak and he had tremor of the limbs, tongue and jaw. The right internal rectus muscle was paralysed. The deep reflexes were exaggerated but there was no clonus. The plantar reflexes were flexor. He was still ambulant but was not able to feed himself. His blood pressure was 110/70 mm.Hg. and the heart rate 78 per minute.

Treatment. He was treated with tincture of belladonna or stramonium, but from 1950 he was treated with benzhexol (Artane) 10 mg. thrice daily.

Comment. He suffers from periodic attacks of severe sweating crisis usually late at night or early in the day. During a severe attack he has increased tremor and makes clicking noises with the tongue as it is alternately protruded and withdrawn. The face and upper limbs are flushed but severe cyanosis has occurred during some severe attacks. The sweating is often of such a degree of severity that his garments and bed-clothes are changed every 15 to 20 minutes. The heart rate rises to 120 to 140 per minute. The rise in systolic and diastolic pressures during severe attacks is up to 50 mm.Hg. and 20 mm.Hg. respectively.

PATHOGENESIS OF OCULOGYRIC CRISIS

Various theories as to the pathogenesis of oculogyric crisis have been formulated. It has even been suggested that the tonic deviation of the eyes is a hysterical manifestation. Two theories will however be discussed in detail.

1. The Relaxion-Sleep Mechanism Theory of Hall.

Hall (1931) in his Schoerstein lecture reported on 384 patients with postencephalitic Parkinsonism, 60 of whom suffered from oculogyric crises. He explored the possibility that the eye muscles instead of being in a state of spasm were actually in a state of relaxation.

He observed that in sleep the axis of the eyes is upwards in 54 per cent of cases, forwards in 38 per cent, downwards in only 5 per cent, and to one side in 3 per cent. He also drew attention to the sequence of events when the normal person closes his eyes: when the lids make contact the eyeballs roll upwards. He noted that sleep relieved the crises and also that there is absence of wrinkling of the forehead during crises. He considered that these observations suggested that upward rotation of the eyes is due to a sleep mechanism. He drew a comparison between the movements of the extrinsic ocular muscles and the eyelids in oculogyric crises and actors hurrying off the stage before the fall of the curtain. He suggested that the drawing of the head to the same side as the direction of the eyes is a compensatory action secondary to ocular inhibition. This theory, though /

though ingenious, is unsatisfactory in many respects. The absence of wrinkling of the forehead is not invariable during oculogyric crisis. Its absence however does not prove that it is part of relaxation of the frontalis muscle during sleep. Fig. 9 shows a patient with post-encephalitic Parkinsonism looking upwards voluntarily. No wrinkling of the forehead is seen, perhaps because of rigidity of the muscles of the forehead. There is a suggestion that failure of the eyelids to close when the eyeballs have been rolled upward causes distress: this is not true, for a number of our patients sleep with their eyes partially open and the eyeballs rolled upwards. Further, one such patient has oculogyric crises periodically but not when he has fallen asleep with his eyes open. Again, Case 5 at some stage during oculogyric crisis has marked drooping of the upper lids. The eyes are shut and the patient is unable to open them unless she lifts the lids with her fingers. The "falling of the curtain" does not seem to relieve her of her distress; on the contrary, whenever this occurs she becomes more distressed. Patients with photophobia during crises keep the eyes tightly closed and the eyeballs are rolled upwards, but these circumstances do not cause such patients to go to sleep.

The fact that natural or drug-induced sleep aborts the crisis does not constitute evidence that upward rotation of the eyes during crisis is a sleep mechanism. On the contrary the beneficial effect of sleep is due to the rest it gives to the active parts of the nervous system and the body as a whole, including the extrinsic ocular muscles.

2. /

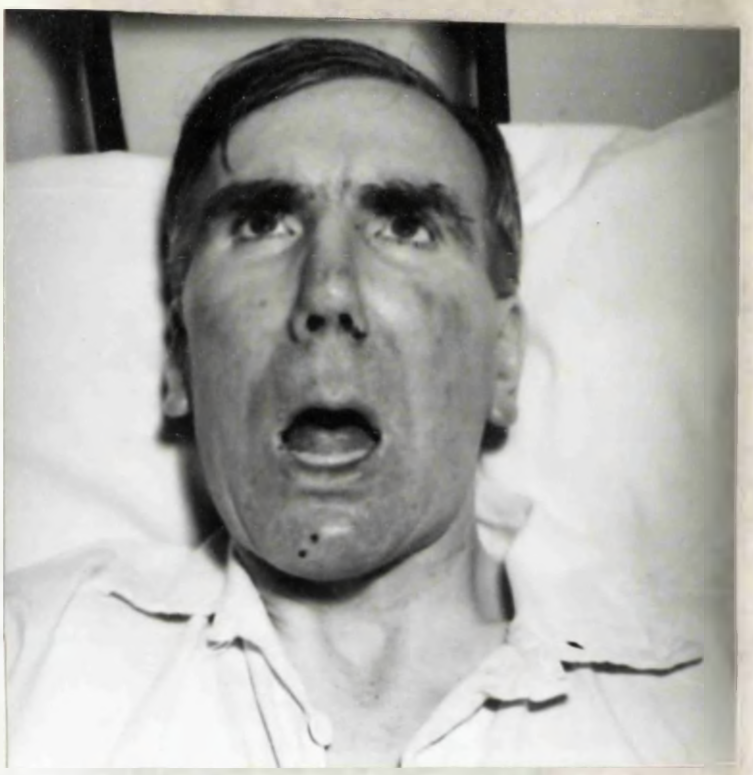


Fig. 9. Patient voluntarily looking upwards. Note absence of wrinkling of forehead.

2. The Compulsive Obsessive Theory of Jelliffe.

Jelliffe (1929) tried to show that oculogyric crisis is a manifestation of compulsive obsessive neurosis in patients who suffer from post-encephalitic Parkinsonism. He gave the histories of four cases and tried to show that some mental or emotional trauma was essential for the initial onset of oculogyric crisis.

During an interview with one patient (No. 4) an oculogyric crisis developed, and the patient said that a million ideas were going through his head - including an urge to kill his brother, etc. Jelliffe believed that there was a repressed feeling in the subconscious which was responsible for the crisis. The rotation of the eyes and the shouting were regarded as ritualistic and secondary to a repressed feeling - usually one of guilt. He believed that there was a "stickiness of thought" (Jelliffe) during the attacks and that this, together with the associated bradykinesia which is usually present, is a correlated part of the akinetic-dyskinetic situation that occurs during oculogyric crisis.

Jelliffe's theory seems to have been quite widely accepted. Curran and Partridge (1955) state that organic disease such as encephalitis lethargica may lead not only to obsessive compulsive phenomena in the ordinary sense but to parallel development in the motor fields such as co-ordinated tics and oculogyric crisis. They believe that these compulsive acts may be ritualistic.

There is no doubt that the tonic rotation of the eyes and the associated /

associated phenomena in oculogyric crises cannot be controlled by the patient, and therefore in the ordinary sense they are compulsive. There is however no evidence that the motor phenomena are ritualistic as a result of repressed feeling such as feelings of guilt.

This theory does not explain why the oculogyric crisis is seen only in post-encephalitic Parkinsonism; and there are a great many people who suffer from the effects of repressed feelings of guilt. It is not uncommon for people to evolve a teleological explanation for the symptoms of their diseases. They convince themselves that the symptoms are due to some wrongdoing which they committed previously. The association of mental or psychological trauma with the initial onset of oculogyric crisis as observed by Jelliffe has not been confirmed in the present series of patients. Most of them can still remember the first attack and they do not associate its genesis with any mental or psychological trauma. On the other hand it may be argued that patients commonly suppress their recollection of their psychological aberration and retain only its "equivalent" in the form of abnormal behaviour. Only careful psychiatric assessment could elucidate such a mechanism.

Stogdill (1934) has attacked the psychoanalyst view that neurosis is due to activity of energised ideas repressed into consciousness. He showed how a remote and irrelevant stimulus can become associated with neurotic behaviour. He then stressed the fact that neurotic behaviour, far from being a ritual, is behaviour that has been learnt.

Apart /

Apart from encephalitis lethargica, Parkinsonism may be due to a variety of causes such as arteriosclerosis, carbon monoxide or manganese poisoning, syphilis, hepatolenticular degeneration, or it may be due to idiopathic paralysis agitans. It is significant that the oculogyric crisis occurs only in post-encephalitic Parkinsonism. It has been stated that oculogyric crises also occur in patients with Parkinsonism associated with cerebral syphilis. Pearson (1927) however reviewed the cases reported: he showed that in all such reported cases (including the single case record which he had published) there was always an initial illness which was not unlike encephalitis lethargica. He therefore concluded that oculogyric crises in such patients had been the sequel to previous attacks of encephalitis lethargica, and that the concomittant syphilis had had no influence in the pathogenesis of the crises.

Recently however "oculogyric crises" have been reported following the administration of drugs of the phenothiazide group (Montgomery and Sutherland 1959, Davis 1959, Bickerstaff and Jacoby 1960). This type of oculogyric crisis is however different from the Parkinsonian form in that spasm of the neck muscles with head rotation - and even opisthotonos - is very common and usually precedes upward eye rotation by up to 30 minutes. Faulkner and Hyde (1958) have shown that electrical stimulation of the midbrain in experimental animals can cause conjugate deviation or rotatory movements of the eyes associated with opisthotonic movements. It may be therefore that these drugs produce similar /

similar effects by actions on the same zones of the midbrain. It should however be noted that oculogyric crises have not been seen in patients with drug-induced Parkinsonism.

Why then is oculogyric crisis confined to post-encephalitic Parkinsonism? Pathological studies (McAlpine 1926) and others have shown that although the inflammatory process may be widespread and involving the cerebrum, the midbrain and pons bear the brunt of the disease. The most significant pathological changes are the degenerative ones in the substantia nigra. In the other forms of Parkinsonism the lenticular nucleus bears the brunt of the disease process.

Clinically palsy of the 3rd, 6th and 7th cranial nerves are frequently seen in post-encephalitic Parkinsonism. Palsies of these nerves from the midbrain and pons are very rare in the other types of Parkinsonism. One may therefore conclude that an important difference between the two forms of Parkinsonism (postencephalitic and non-postencephalitic) is that the former is primarily due to an upper brain stem lesion while the latter is due to lesions in the lentiform nucleus.

Recently Shanzer and Bender (1959) studied the effect of brain stem lesions on oculomotor response to caloric stimulation and found that defects in nystagmus and tonic deviation of the eyes occurred as compared with the response in the normal animal. They found, for instance, that in a monkey with a superior brain stem lesion on one side /

side there was a defect in tonic deviation of the eyes to the side opposite to the side of the lesion. They also found that, on bilateral caloric stimulation, only upward tonic deviation of the eyes occurred and nystagmus, when present, had its fast component upwards. This oculomotor response is not unlike the tonic eye movements and nystagmus seen during oculogyric crises.

The effect of midbrain lesions on muscle tone has been widely studied in experimental animals. Mettler and Zimmerman (1943) found that in cats lesions above the level of the red nucleus gave rise to contralateral rigidity, while ipsilateral rigidity was produced by lesions of the tegmentum below this nucleus. Hardy and Stevenson (1957) reported a case of unilateral syringomesencephalia involving the substantia nigra. This patient had signs of Parkinsonism on the contralateral side. Our observations on this series of patients shows that in a majority of cases, where a predominant unilateral rigidity and lesion of the nerves to the extrinsic ocular muscles are present in the same patient, the cranial nerve lesion is on the contralateral side to the rigidity. This explains why when upward and lateral conjugate deviation of the eyes occurs in oculogyric crisis, the direction of movement of the eyes is usually away from the more rigid side of the body. Thus if the patient's right side is more rigid than the left side, in an oculogyric crisis with upward and lateral movements the resultant deviation of the ocular axes will be to the left side.

A previous study of post-encephalitic Parkinsonism was carried out /

out by Crow in 1949 working in this hospital (Stobhill General Hospital, Glasgow). About 60 per cent of the patients who are now in the "post-encephalitic wards" were included in Crow's series (Crow, 1949). He reported on the effect of various afferent stimuli (such as spraying of the side of the neck with ethyl alcohol, sniffing strong ammonia and caloric vestibular stimulation) on eye movements in patients suffering from post-encephalitic Parkinsonism. He found that he was able to induce oculogyric crisis only by caloric vestibular stimulation.

Study of the various ocular abnormalities in this series of patients shows that 75 per cent of the 20 patients suffering from oculogyric crisis have nystagmus; but of the 40 patients who have neither oculogyric nor sweating crises only 5 per cent have nystagmus (Table 2). In the group with oculogyric crisis nystagmus was ordinarily present in 9 of the 20 patients (45 per cent), and this was increased to 15 (75 per cent) when the patients were observed during crises (Fig. 10). True vertigo was complained of by 8 of the 20 patients (40 per cent) during attacks of oculogyric crisis. The vertigo took various forms, for example, a tendency to fall to one side, apparent rotation of objects, and the sensation of seeing the floor advance towards the patient. No case of true vertigo was seen in the other two groups of patients. Dizziness in the ordinary sense was however fairly evenly distributed in the three groups. Crow was unable to correlate liability to oculogyric crises and the presence of nystagmus. /

GROUPS OF PATIENTS	TOTAL NUMBER	NUMBER OF PATIENTS WITH			
		NYSTAGMUS	VERTIGO	WEAKNESS OR PARALYSIS OF EXTRINSIC EYE MUSCLE	RECENT DIPLOPIA
OCULOGYRIC CRISIS	20	15	8	5	6
SWEATING CRISIS	9	2	0	5	3
WITHOUT OCULOGYRIC OR SWEATING CRISES	40	2	0	5	2

TABLE 2. Relative incidence of vertigo, nystagmus and other ocular lesions in the various groups of the 67 patients.

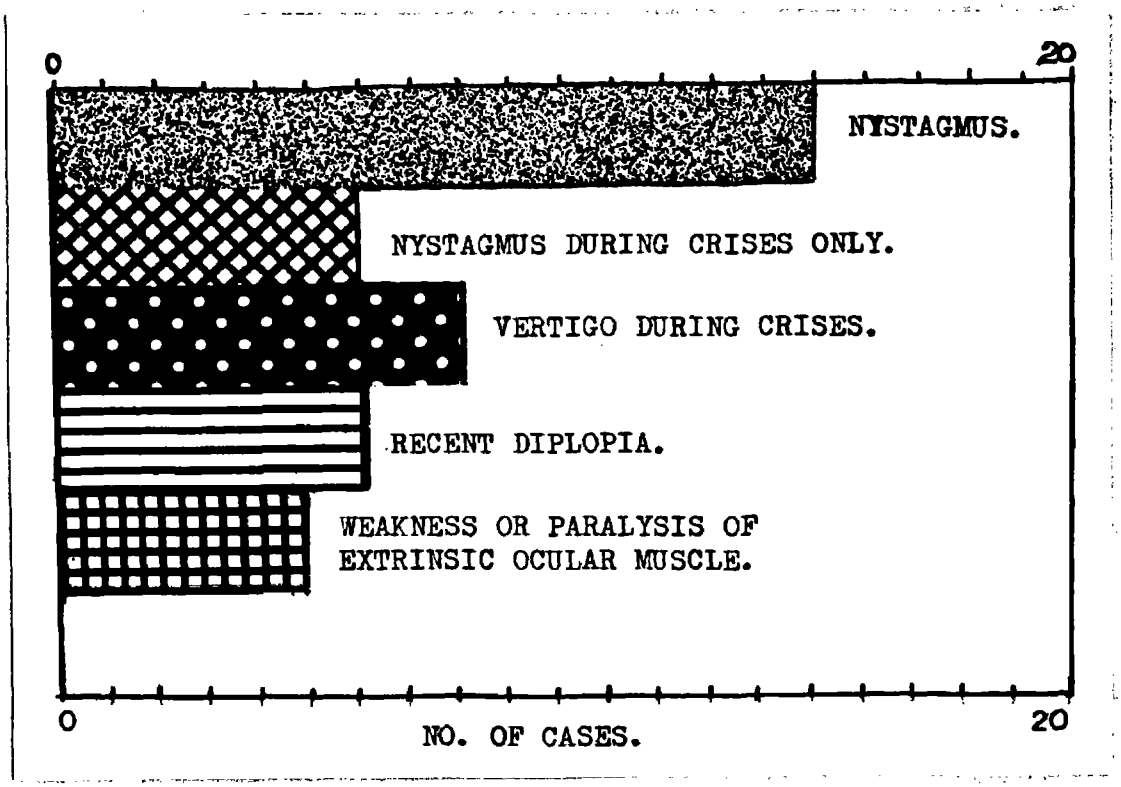


Fig. 10. The relationship between vertigo and certain abnormalities of ocular movement in 20 patients with oculogyric crises.

nystagmus. However this may be attributable to the fact that his criteria for the diagnosis of oculogyric crisis differed from the criteria adopted by the present writer: Crow includes patients who showed staring without deviation of the ocular axes. Again in the earlier paper, no account is taken of the fact that patients normally free from nystagmus may show this abnormality during oculogyric crises.

There is no evidence of cerebellar dysfunction in this group of patients. In view of the prevalence of nystagmus in these patients with oculogyric crisis and the presence of vertigo in a fair proportion during oculogyric crisis, one may therefore conclude that the vestibular apparatus (with special reference to its pathway and connections in the brain stem) is involved in these patients with oculogyric crises.

Examination of the auditory canals in the whole series revealed that 40 of the 67 patients had grossly excessive quantities of hard wax completely blocking one or both ears. In most of them the wax was black - almost tarry in appearance - but in a few it was creamy white. The findings on auriscopic examination appeared to be of considerable importance when reviewed in relation to the total clinical picture. It is of interest to note that most of the patients with little or no wax in their ears were those with minimal signs of Parkinsonism or had perforated eardrums (Tables 3 and 4). It seemed possible therefore that the finding of a greatly increased secretion of wax in the auditory meatus was a sequel to post-encephalitic Parkinsonism. /

TABLE 3.

No.	Name	Age	Degree of Rigidity	Eye Lesion	Degree of wax R. Ear	Degree of wax L. Ear	Crises
1.	J.Bla	62	moderate	none	2	2	none
2.	J.Bel	62	mild to moderate	none	2	1	none
3.	J.McC	50	moderate	vertical nystagmus on movement	2	2	none
4.	D.Gor	57	moderate	vertical and horizontal nystagmus on movement.	1	2	sweating crisis
5.	A.Ead	46	severe	none	2	2	none
6.	J.McF	46	severe	none	1	2	"screaming turns" (very infrequent)
7.	N.San	47	moderate	none	1	1	none
8.	H.Dev	48	severe	nystagmus only during oculogyric crisis.	1	2	oculogyric crisis
9.	T.Gal	48	mild	none	0	0	none
10.	J.Smi	53	moderate	none	1	2	none
11.	J.McI	58	moderate	none	1	2	none
12.	J.McM	50	moderate	Dissociated eye movements. Diplopia.	1	2	sweating crisis
13.	H.War	63	moderate	none	1	2	none
14.	J.Esp	50	moderate	none	2	1	none
15.	R.Pra	42	moderate	Diplopia. Dissociated eye movements. ? slight weakness of right internal rectus. Nystagmus only during crisis.	2	1	oculogyric crisis mild sweating at times.
16.	M.Law	46	severe	horizontal and vertical nystagmus on movement. Some weakness of right internal rectus.	2	1	sweating crisis
17.	R.Bro	51	severe	none	2	1	none
18.	J.Dea	56	moderate	none	½	0	none
19.	C.Han	50	moderate	some dissociated eye movements.	2	1	none except for eye staring
20.	P.Cam	42	severe	weakness both internal recti. Dissociated eye movements.	2	2	none

No.	Name	Age	Degree of Rigidity	Eye Lesion	Degree of wax R.Ear	Degree of wax L. Ear	Crises
21.	J.Cam	57	moderate	Diplopia 3rd nerve palsy right side. Bilateral ptosis - more on right.	1	2	sweating crisis
22.	P.Cad	45	moderate	Horizontal and vertical nystagmus on movement. Dissociated eye movement. Diplopia.	1	0	mild oculogyric crisis
23.	A.Hay	50	moderate	Nystagmus on looking downwards.	0 perforated eardrum	2	mild oculogyric crisis
24.	T.Pow	56	moderate	Diplopia.	1	2	Eye staring mainly but occasionally has true oculogyric crisis
25.	J.McE	42	mild	none	0	0	none
26.	J.Nim	47	moderate	Difficulty in moving the eyes without moving the head.	0	1	patient has hemi ballismus He has Eye staring with head retraction.
27.	T.Wyp	54	mild	none	1	1	none
28.	C.Fea	55	mild	none	1	0	none except for eye staring
29.	D.Vil	48	mild	none	0	0	none
30.	W.Sha	53	moderate	none	½	2	oculogyric and sweating crises
31.	T.Gar	37	severe	Weakness of all movements. Cannot sustain eye movement except for forward gaze.	0	0	none
32.	F.Wal	47	moderate	none			none

TABLE 3. To show details of ocular lesions, degree of rigidity and excess wax in the ears and type of crisis in the 32 male patients.

(Pupillary lesions were not included as the patients were on drug therapy for Parkinsonism).

NOTE: 0 = no wax at all
1 = moderate degree of excess wax
2 = complete blockage of the external auditory meatus.

TABLE 4

No.	Name	Age	Degree of Rigidity	Eye Lesion	Degree of Wax R. Ear	Degree of Wax L. Ear	Crises
1.	M.Dob	56	severe	none	1½	2	none
2.	K.Has	45	severe	none	1½	2	none
3.	C.Ros	71	moderate	none	2	2	none
4.	C.Jon	78	moderate	none	2	2	none
5.	A.McQ	44	moderate	Vertical nystagmus.	2	2	oculogyric vertigo sometimes during crisis
6.	M.Cal	71	moderate	none	0 perforated eardrums	0	none
7.	M.Fay	48	mild	none	0	0 perforated eardrum	none
8.	A.Bis	53	severe	nystagmus in both directions on movement.	½	1	oculogyric crisis
9.	A.Niv	41	severe	some weakness of left external rectus. Horizontal nystagmus on movement.	1	0	"screaming turns"
10	C.McK	57	severe	Paralysis R. internal rectus. Vertical and horizontal nystagmus on movement.	2	2	oculogyric crisis. Vertigo sometimes present.
11.	J.Hug	50	mild	none	0	0	none
12.	R.Gra	52	moderate	nystagmus at rest. Diplopia.	1½	2	oculogyric crisis. Vertigo sometimes present. Diplopia worse during crisis.
13.	R.Cai	62	severe	none	2	2	oculogyric crisis.
14.	M.Fea	62	severe	none	2	2	breath holding attacks.
15.	M.Cra	40	mild	nystagmus during crisis only.	1	1	oculogyric crisis. Diplopia and mild vertigo during crisis.
16.	A.Sin	70	moderate	none	1	1	none
17.	M.McC	48	mild	Cannot move R. eye to full range in both directions.	0	½	none

No.	Name	Age	Degree of Rigidity	Eye Lesion	Degree of Wax R. Ear	Degree of Wax L. Ear	Crises
18.	C.Sco	74	moderate	none	0	1	none
19.	A.McL	54	severe	nystagmus during oculogyric crisis only.	1½	2	oculogyric crisis
20.	A.Tan	51	severe	none	1½	1½	none
21.	A.Pol	54	severe	? some weakness R. lateral rectus. Nystagmus only during oculogyric crisis.	2	2	oculogyric crisis
22.	E.McG	54	moderate	none	2	1½	sweating crisis
23.	A.Mel	49	mild	none	0	0	none
24.	J.Pat	56	moderate	Weakness R.external rectus. Nystagmus only during crisis.	2	2	oculogyric crisis. Vertigo sometimes present. mild sweating crisis
25.	C.McM	55	mild to moderate	Weakness R.internal rectus. Diplopia. Nystagmus only during crisis.	0	1	oculogyric crisis. Diplopia worse during crisis.Vertigo sometimes present.
26.	M.Gil	49	mild	none	0	2	oculogyric crisis with marked photophobia. Vertigo sometimes present.
27.	M.Aus	58	mild	none	0	0	none
28.	R.Mon	39	moderate	none	2	2	sweating crisis
29.	M.McL	56	severe	horizontal nystagmus on movement. Diplopia.	1	2	oculogyric crisis. No vertigo or diplopia during crisis.
30.	A.Car	47	severe	weakness both internal recti. Dissociated eye movements. Diplopia.	1½	2	none
31.	H.McG	39	moderate	none	0	½	none
32.	E.McK	56	moderate	none	2	½	none
33.	A.McL	59	mild to moderate	Diplopia occasionally.	½	½	none
34.	C.Bun	50	mild	none	1	½	oculogyric. Vertigo sometimes during crisis.
35.	M.Rei	47	mild	none	2	1½	oculogyric crisis (infrequent). No vertigo or diplopia.

TABLE 4

Details of ocular lesions, the degree of rigidity, the degree of excess wax in the ears, and the type of crisis in the 35 female patients.

(Pupillary lesions are not included as the patients were on drug therapy for Parkinsonism.)

NOTE.

0 = no wax at all

1 = moderate degree of excess wax

2 = complete blockage of the external auditory meatus.

Parkinsonism. This was not entirely unexpected: seborrhoea and a greasy skin are characteristic of this condition (Denny-Brown 1946, and Mackenzie 1927) and it may be that increased activity of the sebaceous glands of the skin is paralleled by an increase in the secretion of wax. It is suggested that the persistence of a gross excess of hard wax in the auditory canals is a possible source of vestibular stimulation capable of inducing oculogyric crisis in patients with suitable brain stem lesion.

It may be concluded that at least two factors are essential before oculogyric crisis can occur, viz:

1. The existence of a particular type of lesion of the brain stem which produces nystagmus without evidence of cerebellar dysfunction. Such a lesion is probably an irritative one situated in the vestibular pathway.

2. Some source of vestibular stimulation such as the presence of hard wax in the external auditory canals in sufficient amounts to cause obstruction to the lumen and tension in the walls of the canals. Other sources of vestibular stimulation, such as revolving while waltzing are capable of precipitating an oculogyric crisis (McCowan and Cook, 1928).

It is of great interest that from theoretical considerations of the effects of lesions of the vestibular nerve and pathway on the movements of the body in vertebrates. Muskens (1927) concluded that the oculogyric crisis in post-encephalitic Parkinsonism is due to a lesion in the posterior commissure in the region of the midline, that is /

is at the area of decussation of the cephalic fibres from the vestibular nuclei.

Duverger and Barre (1921) from a clinical study of the effects of caloric vestibular stimulation in patients suffering from tabes dorsalis and post-encephalitic Parkinsonism, also came to the conclusion that the disorders associated with the eyes (nystagmus, diplopia, weakness of the extrinsic ocular muscles and spasms which lead to fixation of the ocular axes) in these diseases are of labyrinthine origin.

In 4 patients an attempt was made to determine the therapeutic value of removing wax from the auditory canals. The wax was first softened with "Cerumol" and it was then dislodged by syringing. During the following 8 weeks there was no significant reduction in the number of oculogyric crises in these patients, but in one of them the severity of the crises was appreciably diminished.

That the brain stem, especially the midbrain, contains intrinsic co-ordinating mechanisms capable of producing conjugate eye movements, has been observed by various workers and this has recently been confirmed by Hyde and Eliasson (1958) and Faulkner and Hyde (1958). Szentagothai (1950) has shown that there are numerous connections between the labyrinth and the extrinsic ocular muscles.

The time interval between the acute illness of encephalitis lethargica and the onset of oculogyric crisis is very variable: it may be a few years or as long as 22 years. The explanation may lie in /

in circumstances which in turn depend upon the different factors concerned in the pathogenesis of oculogyric crises and to which reference has been made above. Although reactivation of the infective process is denied by various workers (MacKenzie 1927, McPhater 1942), there is no doubt that the disease may be progressive and that it may extend in the upper brain stem and involve zones and tracts that were not originally involved.

Anatomy and Physiology of Emotion.

As emotional excitement (occasionally depression) is common - particularly in severe oculogyric crises - the anatomical and physiological aspects of emotion will be discussed briefly in the hope that this may throw some light on the pathogenesis of oculogyric crises.

The concept of emotion however has for long been a matter of controversy among psychologists. There has been much confusion as to what "emotion" really means. Duffy (1934) suggested that the term "emotion" should be completely abandoned as the concept does not serve any useful purpose in scientific psychology, her main objection being that no difference can be found between emotional and non-emotional responses.

Cannon (1927) and Bard (1934) however showed that emotion implied two things: (1) a way of acting, or the expression of emotion; (2) a subjective experience - which includes the neural processes which lead to emotional awareness.

In attempting to localise the area of the brain concerned with emotional expression, Cannon and Britton (1925) found that even the decerebrate /

decerebrate animal is able to show expression or to exhibit behavioural patterns commonly associated with emotional excitement. Thus these animals were capable of snarling and clawing accompanied by dilatation of the pupils and greatly increased arterial blood pressure and heart rate. Bard (1934) demonstrated that the presence of the thalamus is not essential for the occurrence of the phenomenon of sham rage. He concluded from his study that the expression of emotion originates from activities of the posterior hypothalamus and possibly the mid-brain.

Electrical stimulation of the hypothalamus (Kabat, Anson and Magoun 1935) gave rise to a marked increase in arterial blood pressure, pupillary dilatation, sweating, etc. Redgate and Gellhorn (1956) demonstrated the tonic vasomotor function of the hypothalamus, showing that among the functions of the posterior hypothalamus is that of raising the blood pressure and increasing the heart rate; it also appears to exercise some control over the medullary vasomotor centre.

The rise in blood pressure, tachycardia, paroxysms of sweating, irregular respiration, tremor, flushings of the face and conjunctiva, and even increased salivation seen during oculogyric crises are all recognised accompaniments of emotional expression and are probably mediated by diencephalic over-activity.

Other areas of the brain however have been shown to have an effect on the blood pressure, heart rate and respiration. Smith (1945), and Ward (1948) using experimental animals - and later using human /

human subjects Pool and Rasohoff (1949) - showed that stimulation of the cingulate gyrus led to a rise in blood pressure, to changes in respiratory rates, but more frequently to a fall in heart rate. Whitty (1955) came to somewhat similar conclusions when he studied the effect of anterior cingulectomy on patients with anxiety neuroses or obsessional states. A significant rise in blood pressure and heart rate, and the onset of irregular respiration have all been shown to occur following stimulation of the temporal lobe or the orbital surface of the frontal lobe (Kaada et al. 1949; Kaada and Jasper 1952; Van Buren 1958; Degaldo and Livingston, 1948).

Although the hypothalamus, anterior thalamic area, cingulate gyrus, hippocampus and their interconnections may all be involved in the elaboration of central emotion and in the production of emotional expression (Papez 1937), the "emotional" accompaniments of oculogyric crises (hypertension, tachycardia, congestive phenomena, irregular respiration, dilated pupils, excessive salivation and shouting) are comparable with pseudo-affective state (sham rage) of Cannon and Britton (1925) except that the post-encephalitic patient is conscious of what is happening. The inhibitory cortical fibres from the cerebral cortex to the diencephalon are partially damaged as a result of the widespread inflammatory process resulting from encephalitis. He is therefore deprived of the full measure of inhibition normally available to counteract the sham rage syndrome generated in the diencephalon.

Numerous /

Numerous collateral connections from the afferent pathways, especially from the 8th nerve to the reticular system of the brain stem, the subthalamus, the hypothalamus and the ventromedial portion of the thalamus, have been demonstrated by Starzyl, Taylor and Magoun (1951), and French, Amerongen and Magoun (1952). The stimulation of the reticular system of these areas from vestibular stimulation is probably responsible for the tachycardia, congestive states and other disturbances which accompany oculogyric crisis. It can hardly be doubted that rotation of the head and neck is the sequel to vestibular stimulation.

The Role of Emotion in Precipitating Oculogyric Crises.

The effect of emotion as a precipitating factor has been observed in this series of patients: the conclusions are similar to those of previous workers (Bramwell, 1928; McCowan and Cook, 1928).

In analysing the factors concerned in the pathogenesis of oculogyric crises a distinction must be made between the initial phase and a later stage of recurring crises. In the light of information gathered during the present study it is clear that the first crisis is not the direct result of emotional upset or mental trauma. The onset of an oculogyric crisis is almost certainly due to vestibular stimulation. The rather sudden and spontaneous tonic rotation of the eyes may well generate emotion and indeed fear, anxiety or grief, and the manifestations of emotional instability already described. The patient may try to devise a teleological explanation of the whole disturbance /

disturbance and thus comes to correlate the rolling of the eyes with some particular pattern of thought - likely enough to be associated in some cases with the feeling of guilt. As a result of a temporal relationship between the eye movements, the subjective experience on the one hand and some environmental factors (such as the presence of patients' relatives, meal times, particular types of food) on the other hand, an association develops between them: in other words the pattern of a conditioned reflex is established. The environmental factors however are quite irrelevant to the original mechanism whereby the crises were generated. Recurring oculogyric crises in a particular environment have the effect of conditioning the patient to these environmental factors or to certain thought processes and thus create a spurious concept of cause and effect. When conditioning has occurred, these thought processes and "irrelevant" environmental circumstances may indeed assume major importance, for the patient may become the victim of suggestion based upon a complex conditioned reflex. Thus adventitious circumstances can eventually provide powerful sensory impulses precipitating motor upsets (oculogyric crises and all that goes with a crisis), notwithstanding the fact that the first crisis in the patient's experience was purely somatic in character.

The main thesis presented in this section to account for the pathogenesis of oculogyric crisis is essentially somatic. That is to say the crises are the outcome of vestibular stimulation dependant on physical /

physical conditions. Nevertheless it must be considered that the clinical picture is complicated by the undoubted importance of psychological factors. Thus in the present series there is ample confirmation of the views of previous workers who stressed the significance of emotional disturbances which predispose to the onset of oculogyric crises. It is possible to visualise this sequence of events as a lowering of the threshold of the mechanism governing upward conjugate deviation of the eyes in oculogyric crisis. The lowered threshold may be due to neuronal activity in the diencephalon and upper brain stem occasioned by the subjective aspect of emotion.

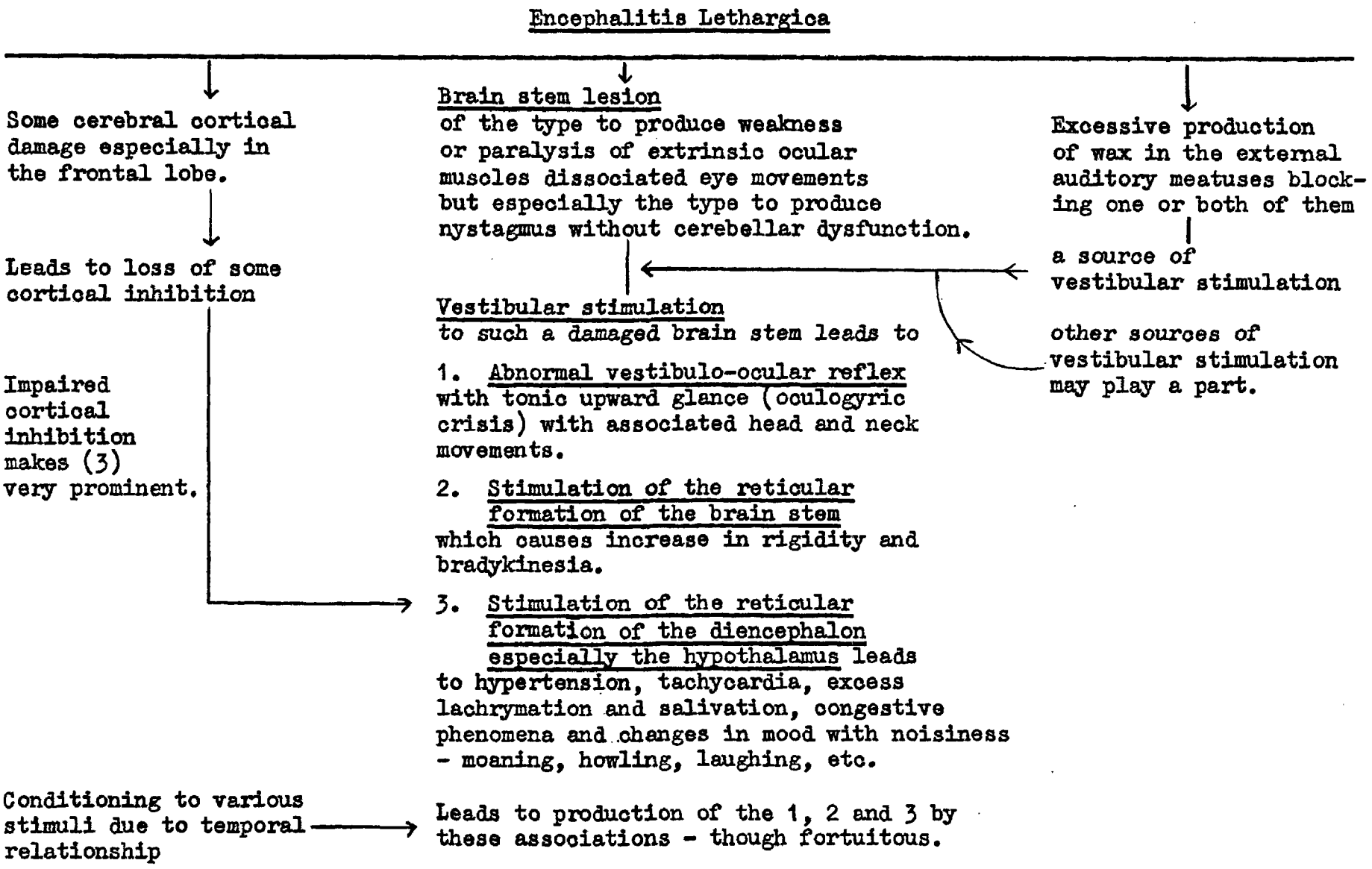


Fig. 11 To illustrate the pathogenesis of oculogyric crises and associated phenomena

SUMMARY

A study of 67 patients with post-encephalitic Parkinsonism revealed three types of crises: they can be described as oculogyric, sweating and breath-holding.

The clinical accompaniments of oculogyric and sweating crises are described. Attention is drawn to the vasomotor changes which occur during severe oculogyric and sweating crises and to changes in mood during oculogyric crises.

The pathogenesis of the oculogyric crisis is discussed. It is suggested that ocular deviation is the consequence of a vestibulo-ocular reflex in patients with brain stem lesions involving the vestibular pathway. The emotional changes which accompany oculogyric crises are probably the result of stimulation of the diencephalon.

The role of emotion in precipitating oculogyric crises is confirmed. When emotion is known to play a part, it is suggested that the mechanism includes a conditioned reflex. Alternatively it may be that the onset of emotional disturbance sometimes permits activity in the vestibulo-ocular reflex; activity which in the non-emotional state is materially inhibited.

CHAPTER III

DRUG THERAPY IN THE CRISES OF POST-ENCEPHALITIC PARKINSONISM

In the preceding chapter the manifestations of the various types of crises in post-encephalitic Parkinsonism were described and the pathogenesis of oculogyric crisis was discussed. This chapter will deal with the problem of drug therapy in oculogyric and sweating crises.

In the past it was the practice in the two post-encephalitic wards of this hospital, to resort to barbiturates such as amylobarbitone, used essentially as powerful hypnotics and administered orally for the treatment of these crises. This therapeutic approach to the emergency presented by patients in crisis failed to do justice to the predominantly motor character of the disorder. It seemed preferable to use sodium phenobarbitone administered parenterally, for this is recognised to be the drug of choice in preventing and suppressing epileptiform seizures by depressant effect upon the motor cortex of the brain.

METHOD AND MATERIAL

A preliminary study was made of the relative merits of sodium amylobarbitone (200-300 mg. by mouth) and phenobarbitone (200 mg. intramuscularly /

intramuscularly as the sodium salt). Subsequently the method of parenteral administration of sodium phenobarbitone was modified: 150 mg. was given intravenously and the remainder (50 mg.) was then injected intramuscularly; this method was used while studying 9 patients with severe oculogyric crises, and 4 patients with sweating crises - in two of whom the crises were very severe. The effect of the drug on the various manifestations of a crisis was recorded every 10 minutes: the phenomena noted were the direction of the deviation of the eyes, ability to move the eyes voluntarily in both vertical and horizontal directions, the state of the pupils, degree of rigidity and tremor, heart rate, level of blood pressure, salivation, sweating and mood. As a control procedure, on 6 occasions, 4 patients who were in crisis received normal saline intravenously and intramuscularly. The combined intravenous and intramuscular phenobarbitone therapy has been given in 49 instances of severe oculogyric crisis and in 10 severe sweating crises.

It is emphasised that all the patients included in this study were deliberately selected because of the severity and long duration of their crises. Table 5 shows the approximate duration of their untreated crises in each case.

The effect on oculogyric crisis of 0.6 mg. of atropine sulphate and 0.6 mg. of hyoscine hydrobromide made up to a 3 ml. solution in sterile water and injected intravenously was subsequently studied. Hyoscine was given on 11 occasions to 4 patients (W.S.; J.P.; M.G.; and /

Name	Sex	Age (yr.)	Type of crises	Duration if untreated (hr.)	No. of times parenteral phenobarbitone therapy given	No. of failures or relapses	No. of times placebo injections given
J.C.	M	57	Sweating (v. severe)	2-4	7	1 failure (partial)	—
J.M.	M	50	Sweating (v. severe)	2-4	3	1 relapse	—
W.S.	M	53	Oculogyric (occasional sweating)	4-10	7	1 failure	2
H.D.	M	48	Oculogyric	3-6	3	—	—
J.P.	F	56	Oculogyric (occasional sweating)	6-12	7	—	—
M.C.	F	40	Oculogyric	3-6	8	1 relapse	2
C.M.	F	55	Oculogyric	3-5	3	—	—
M.G.	F	49	Oculogyric	4-6	14	1 failure	1
M.R.	F	47	Oculogyric (very infrequent)	3-4	1	1 relapse	—
R.G.	F	52	Oculogyric	3-5	2	—	1
A.M.	F	54	Oculogyric	5-10	4	—	—

TABLE 5. To show the approximate duration of the untreated crises, and the number of times sodium phenobarbitone by combined intramuscular and intravenous injection was given in each case. (Reproduced from Onuaguluchi (1961) Soot. med. J. 6 368).

and A.Mc.), and atropine on 4 occasions to 2 patients (J.P. and M.G.). In two patients (J.C. and J.P.) the effect of intravenous atropine sulphate (0.6 mg.) on sweating crisis was studied on three occasions.

RESULT OF TREATMENT

1. OCULOGYRIC CRISES

Preliminary studies showed that oral amylobarbitone 200-300 mg. or intramuscular sodium phenobarbitone 200 mg. sufficed to control crises which were mild or even moderate in severity. On the other hand, in patients who suffered from severe oculogyric crises, barbiturates (given orally or intramuscularly) failed to give relief unless the drug induced sleep.

It was concluded that the success of this treatment depended upon the hypnotic action of the drug when used as described above: on wakening from sleep the ocular axes had resumed their normal position. If sleep was not induced, deviation of the eyes persisted and the crisis often lasted for several hours. For example, in one patient who was suffering from a severe oculogyric crisis, the symptoms were still present 6 hours after injecting 200 mg. sodium phenobarbitone intramuscularly.

The intravenous administration of sodium phenobarbitone has been successful in nearly all cases in aborting severe oculogyric crises and sweating crises. Characteristically, in a severe oculogyric crisis /

crisis the blood pressure is raised and the heart rate is increased; but 10 minutes after receiving sodium phenobarbitone intravenously both the blood pressure and the heart rate had returned to their pre-crisis levels. Patients did not experience subjective improvement until 10 to 20 minutes had elapsed. The central position of the eyes and normal voluntary ocular movements were not restored until 20 to 40 minutes after the injection. Spontaneous nystagmoid movements with the rapid phase upwards were frequently seen just before the eyes became normal. It was usually well over one hour before flushing of the face disappeared and congestion of the conjunctiva lasted even longer. Slight suffusion of the conjunctiva was occasionally seen as long as 3 hours after the intravenous injection of the sodium phenobarbitone. The effect of parenteral therapy on bradykinesia (unwillingness to move) was very striking. On many occasions patients who had been reluctant to move at all showed a strong desire to be up and about soon after receiving sodium phenobarbitone intravenously. On two occasions one patient (W.S.) got up and played billiards with his usual degree of skill about one hour after receiving this treatment for oculogyric crises.

Fig. 12 shows the effect of giving 200 mg. of sodium phenobarbitone by the combined route in Case 1 during a severe oculogyric crisis. The fairly rapid effect on the blood pressure, cardiac rate, salivation, noisiness, rigidity and (to a lesser extent) on tremor is demonstrated.

A /

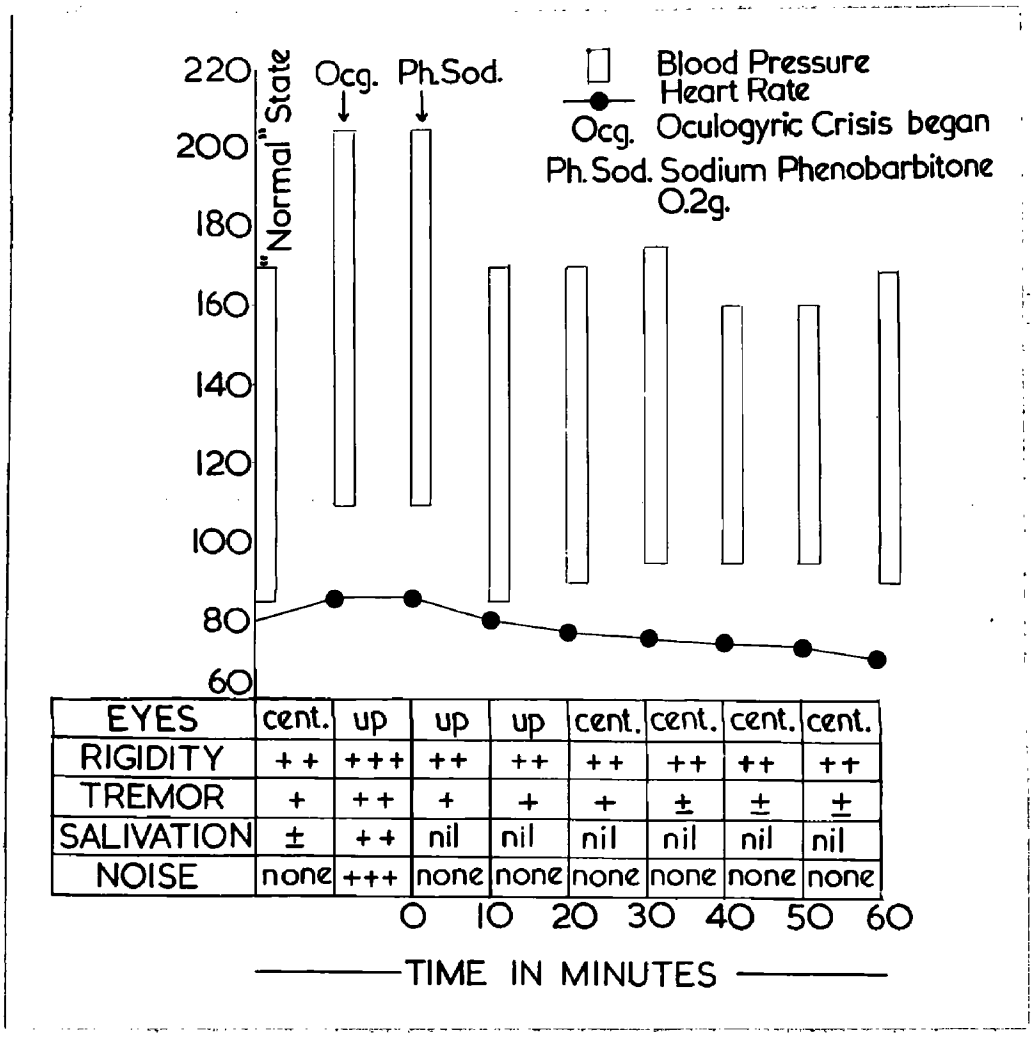


Fig. 12. Case 1. Effect of sodium phenobarbitone 0.2g. given intravenously in an established and severe oculogyric crisis.

A more detailed account can now be given of the ocular findings before and after treatment in an individual patient: Case 1.

(a) Condition before Treatment: The eyes were rotated upwards and to the right. She was unable to bring the eyes down or to move them to the left. The pupils were small; they reacted sluggishly to light but not to accommodation. The conjunctivae were injected but there was no photophobia. She was very noisy.

Sodium phenobarbitone was then given parenterally (dose, etc. - as described above).

(b) Condition after 10 minutes: The eyes were still directed up and to the right and could not be brought down or moved laterally. The pupils were now slightly bigger and reacted well to light but not to accommodation. The conjunctiva was still injected. She was now quiet; but she said she did not feel any better.

(c) After 20 minutes: The ocular axes were now shifting downwards; she could move her eyes in both the vertical and the horizontal direction, but these movements were not sustained for more than 2 seconds. No further change had occurred in the state of the pupils or of the conjunctiva. She was quiet; and she said she now felt better.

(d) After 30 minutes: The eyes were central although there was a tendency to upward deviation, giving rise to nystagmoid movements. Voluntary movements of the eyes in all directions were however more sustained. The state of the pupils and conjunctiva were unchanged /see (b)/

(e) /

(e) After 40 minutes: The eyes were now central and there was no tendency to upward deviation. Movement in all directions was good and well sustained. The pupils were now of normal size and reacted well to light. The face and conjunctivae were less flushed. She felt much better and was now smiling.

Intravenous hyoscine hydrobromide (0.6 mg.) was successful in all cases in controlling oculogyric crises. The ocular axes returned to normal in 10 to 20 minutes. This compares with 20 to 40 minutes when sodium phenobarbitone was given by the combined route. The blood pressure and the heart rate also returned to the pre-crisis level within 10 minutes after the injection. Hyoscine however aggravated the bradykinesia which is often present during oculogyric crises. The patients seemed dazed for an hour after the injection, and in the first 40 minutes of this phase they responded poorly if at all to commands. Drowsiness was a side-effect seen in all cases, but the hypnotic action was not considered to be responsible for the effect of the drug in abolishing ocular deviation: normal movement of the eyes was restored before the onset of drowsiness. Another disagreeable side-effect was the excessive dryness of the mouth, tongue and throat which made speech and eating difficult.

Atropine sulphate (0.6 mg.) administered intravenously was not as effective as hyoscine or sodium phenobarbitone. The reduction of blood pressure to pre-crisis level was usually delayed for 20 to 30 minutes. The cardiac rate was also unaffected for 20 minutes after the /

the injection; in fact a rise in the heart rate was sometimes seen in the first 20 minutes. In one of the 4 instances the eyes were still rotated upwards one hour after injecting the drug. On the other three occasions the eyes were central 20, 30 and 40 minutes respectively after administering the drug. Centralisation of the eyes was accompanied by a fall of blood pressure, and the heart rate also tended to fall to the pre-crisis level. Excessive dryness of the mouth, tongue and throat was again a common complaint.

2. SWEATING CRISES

(a) Sodium phenobarbitone.

In treating severe forms of sweating crisis with sodium phenobarbitone intravenously it was again noticed that the blood pressure and cardiac rate reverted to their pre-crisis levels within 10 minutes. Sweating, however, although considerably reduced in the first 10 minutes, usually continued for another 10 to 20 minutes. Alleviation of muscular rigidity and tremor was noted - as in oculogyric crises.

Figure 13 shows the effect of injecting sodium phenobarbitone in a very severe sweating crisis in Case 3. Perceptible sweating had ceased 30 minutes after administration of the drug. Although there was a rapid fall in blood pressure and cardiac rate, the levels were still above the pre-crisis level even after 40 minutes. A relapse occurred 90 minutes after the injection; sweating, tachycardia and a rise /

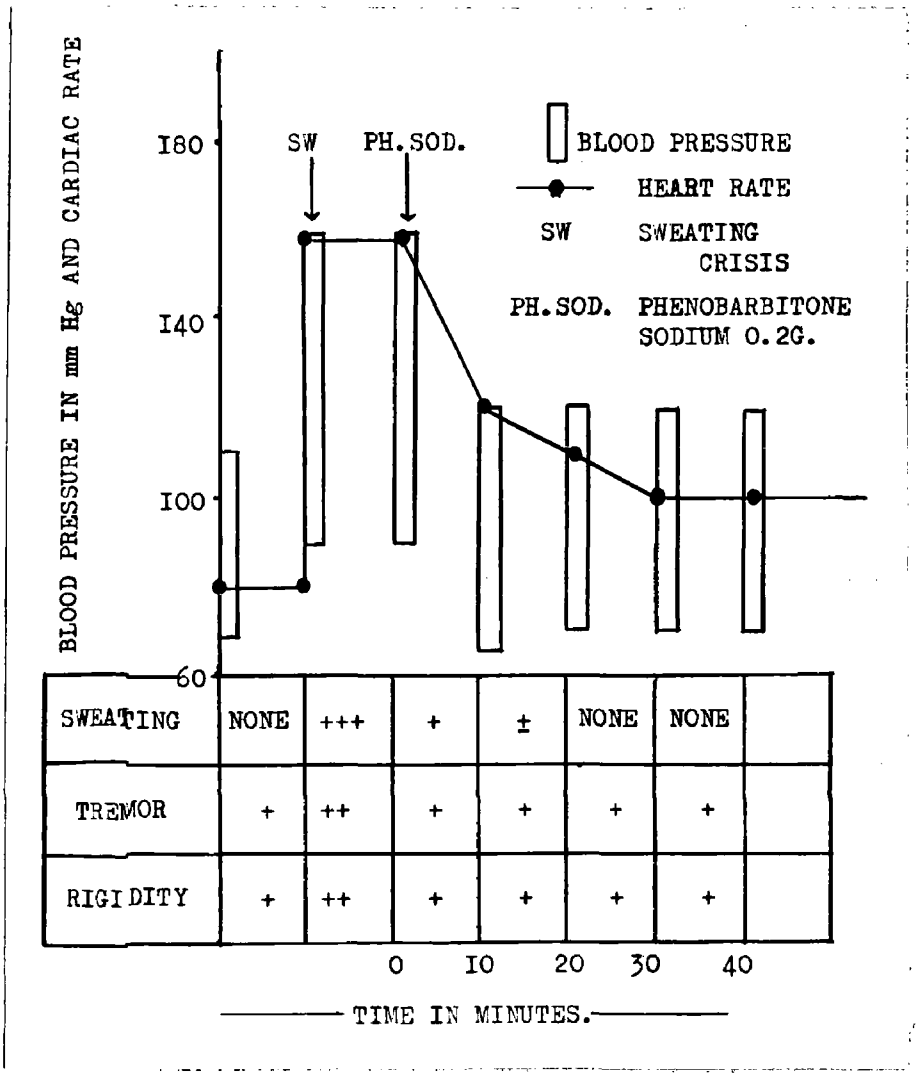


Fig. 13. Case 3. Effect of sodium phenobarbitone 0.2g. given intravenously during a severe sweating crisis.

The systolic blood pressure and the heart rate did not return to normal levels under the influence of the drug; the crisis recurred 90 minutes later - but in a milder form.

rise in blood pressure recurred, but these abnormalities were now less severe.

This phenomenon of 'escape' from the effects of phenobarbitone was one of considerable interest and significance. It has been recorded on three occasions while studying this group of patients. All were suffering from very severe crises - one in a sweating crisis (Case 3) and two in oculogyric crises. 'Escape' occurred between 60 and 90 minutes after the administration of sodium phenobarbitone. Here again the symptoms during relapse were less severe than in the initial crisis, and they passed off in 1 to 3 hours.

(b) Atropine sulphate (0.6 mg.) given intravenously was a more powerful suppressant of sweating than 200 mg. of sodium phenobarbitone administered by the combined route. The sweating stopped in 10 to 20 minutes. However several undesirable side-effects were observed:

(1) An increase in heart rate (Fig. 14).

(2) Flushing of the skin and a sensation of heat.

(3) At this dose level, excessive dryness of the mouth, tongue and throat occurred. One patient (J.C.) said that the treatment made his tongue "as hard as wood", and he refused to have any further treatment for sweating crises if atropine was to be given.

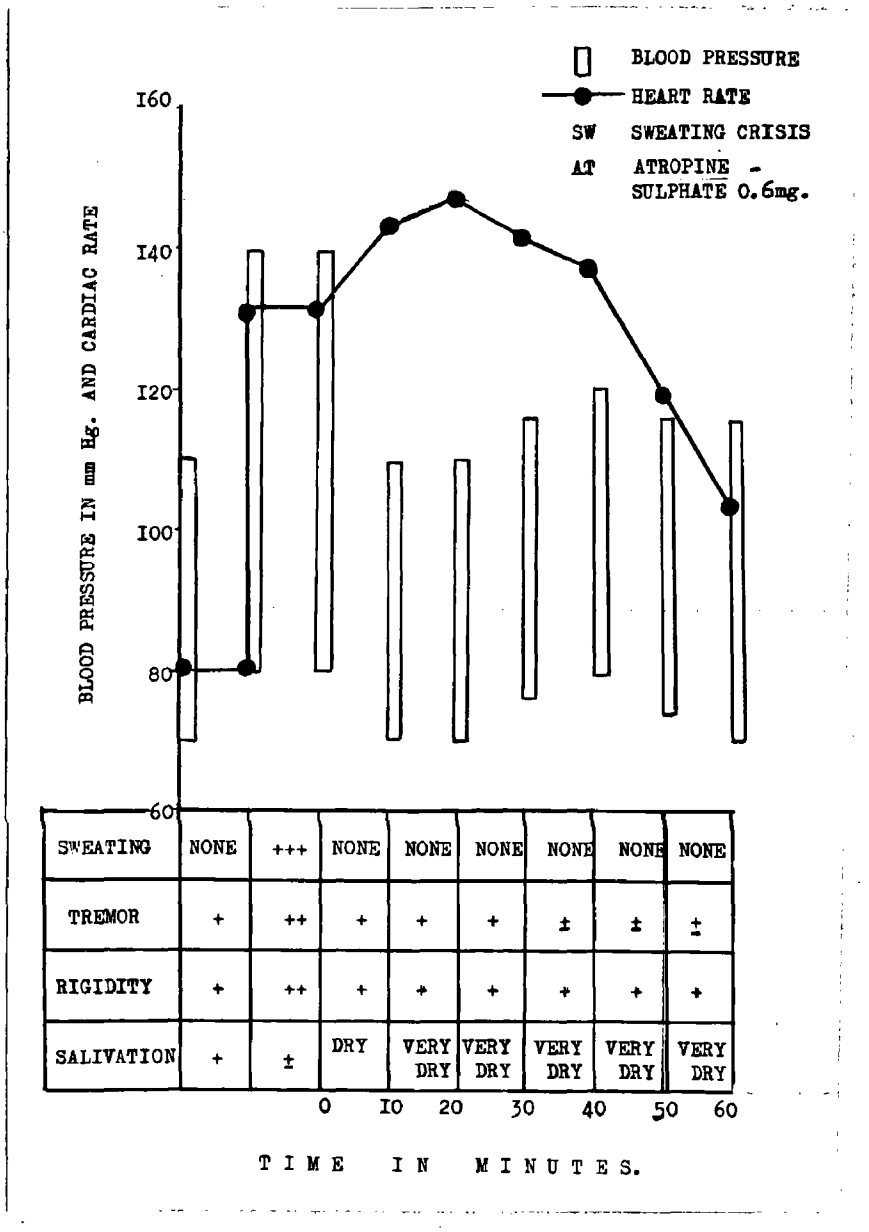


Fig. 14. Case 6.

Effect of atropine sulphate 0.6 mg. given intravenously during a severe sweating crisis.

Note the increase in the heart rate. The patient was more flushed and complained of extreme heat and also of dryness of the mouth and throat.

DISCUSSION

Many factors are involved in the neurological mechanism that precipitates an oculogyric crisis. The influence of volition is apparent from the fact that when the prodromata - or even the actual signs - of a crisis appear, a sharp word of rebuke or a shake of the patient's shoulders (such as might be used for a wayward child) may suffice to abort the attack or to postpone its onset. The phenomenon is perhaps analagous to that of aborting Jacksonian epilepsy by the immediate application of manual pressure to the patient's twitching limb. The suppression of an oculogyric crisis however rarely amounts to more than a temporary inhibition: apparently the stimuli build up again and the signs of crisis become obvious in their florid form. It must also be emphasised that only mild crises are amenable to inhibition by the attendant.

Notwithstanding considerable experience of the influence of suggestion in the treatment of the postencephalitic, it is also apparent that the injection of sodium phenobarbitone intravenously is highly effective in the treatment of severe oculogyric and sweating crises; the dose is 2 - 3 mg./Kg. body weight.

Sodium amylobarbitone given intravenously (150 mg.) has been shown to prevent nystagmus on direct forward gaze (Nathanson et al., 1953). King, Naquet and Magoun (1957) showed that in light doses the site of action of barbiturates is on the central reticular formation of the mid-brain where it blocks the ascending activating influence /

influence of the brain stem reticular formation. Arduini and Arduini (1954) arrived at similar conclusions. French, Verzeano and Magoun (1953) showed that the effect of an anaesthetic dose of sodium pentobarbitone was on centrally located responses in the pons, midbrain and thalamus; these authors also discovered that potentials from the lateral sensory pathways (the lemnisci) were unchanged by the administration of sodium pentobarbitone considerably in excess of the amounts that caused profound changes medially.

An oculogyric crisis has been shown to be most probably due to a vestibulo-oculomotor reflex in patients with certain types of brain stem lesion resulting from encephalitis lethargica. The centre for this reflex is therefore in the upper brain stem. There is probably also marked activation of the reticular formation of the brain stem and this increased activity spreads into the hypothalamus and the thalamus. Presumably a sweating crisis is also caused by discharges from the diencephalon and perhaps also from the reticular formation of the upper brain stem. Phenobarbitone therefore appears to act by blocking afferent impulses (including vestibular impulses) destined to activate the brain stem and diencephalon. Thus the drug may prevent a spread of impulses into the reticular formation at midbrain and diencephalic levels. The ultimate result is that discharges from this zone of the brain are blocked and oculogyric and sweating crises are thus prevented.

The time lag of 20 to 40 minutes after the administration of intravenous /

intravenous phenobarbitone before the eyes were central and normal is interesting. The same interval of time has been observed by Wilson (1959) who studied the protective action of thiopentone on audiogenic seizures in mice. The cause of this time lag is still unexplained. The latent period is similar to that which occurs in normal people after injecting atropine sulphate intravenously: about 10 minutes elapse before the anticholinergic effects become apparent. An additional point of interest - suggesting "conditioned tolerance" to drugs where the recipient suffers from a particular disease - is the fact that sleep was rarely induced by the dose of phenobarbitone given. This was also observed by Nathanson et al (1953). The circumstances are somewhat similar to those existing in the epileptic patient who nearly always tolerates moderate doses of phenobarbitone without suffering from drowsiness - which would almost invariably develop in normal people.

Bradykinesia is practically abolished and this is one of the great advantages of intravenous therapy. The patient is rarely made drowsy and within an hour he can be up; and his gait is not ataxic. As a relapse occurred on three occasions, it would appear that in very severe cases the dose of 200 mg. of sodium phenobarbitone should be injected intravenously to prevent such recurrences.

Burr and Snavely (1926) and de Maar (1956) have shown that the probable site of action of the belladonna group of drugs - hyoscine, atropine and hyoscyamine - is in the diencephalon where they block discharges /

discharges arising from this area. Hohman (1925), McCowan and Cook (1928) found hyoscine administered parenterally to be effective in aborting oculogyric crises and although this has been confirmed in this study, it is claimed that the use of intravenous sodium phenobarbitone is preferable to the parenteral administration of hyoscine for the treatment of oculogyric crisis. Intravenous sodium phenobarbitone reduces or abolishes bradykinesia associated with the crisis; and within an hour of the injection the patient's equanimity is restored, and he wants to be up and about. Hyoscine on the other hand aggravates the bradykinesia; drowsiness is also a common side-effect, during the first hour after injecting the drug the patient is often dazed. Excessive dryness of the mouth, tongue and throat may be a disturbing side-effect after administering hyoscine. In addition Brocklehurst (1953) reported that in the elderly and in patients with Parkinsonism, subcutaneous administration of hyoscine often caused irregular involuntary movements accompanied by extensor plantar responses. These side-effects were not observed however in the patients in the present series.

The use of atropine is not recommended: in the treatment of oculogyric crises it is inferior to hyoscine and to phenobarbitone. Although the two patients treated with atropine did not show signs of further excitement from the drug itself, atropine is classed as a delirifacient, and there obviously is a prima facie case for avoiding its use in post-encephalitics in oculogyric crisis - as excitement attributable /

attributable to this condition often provides an indication for treatment on other lines.

In sweating crises where it might theoretically be regarded as the therapeutic agent of choice, its use may lead to disturbing side-effects: these are flushing of the skin with an accompanying sensation of heat, dryness of the mouth and throat and aggravation of tachycardia in a condition where the heart rate may be as high as 150 beats per minute.

Variations in the potency of hyoscine and of atropine, even in the purest samples (Sollman, 1948; Domino and Hudson, 1959), make their use in clinical trials unsatisfactory and incidentally also accounts for occasional failures (or partial failures) when these alkaloidal salts are used in other fields of medical practice.

Another drug which blocks discharges from the midbrain is phenytoin sodium (Gangloff and Monnier, 1957). It is of limited value in dealing with the crisis once it has developed. It should also be noted that the sodium salt in solution is not suitable for parenteral injection because it is strongly alkaline (Martindale, 1958).

PROPHYLAXIS

1. Barbiturates

Leake (1935) from his experience in a solitary case suggested that methylphenobarbitone (Prominal) given by mouth might be of use in preventing oculogyric crises. Our experience shows that barbiturates orally are not of much value in reducing the frequency of oculogyric /

oculogyric crises, although there is some indication that they have a place in reducing the frequency and the severity of sweating crises. Drowsiness and dizziness are unwelcome side-effects but they are not common. The most disabling side-effect is increasing dysphagia: this is probably a sequel to drowsiness but it occurs very infrequently.

2. Sodium Phenytoin

Sodium phenytoin 45 mg. - 180 mg. orally three times daily was given prophylactically to 5 patients with oculogyric crisis. The results were very discouraging but of great interest. The effects were more noticeable in the 3 female patients. Sodium phenytoin seemed to alter the character of oculogyric crisis. The tonic phase (in which the eyes were rolled upwards and could not be moved in any direction) was now less frequently seen. The nystagmoid phase with the rapid upward phase (or upwards and to one side) was very prominent and lasted for several hours - even up to 24 hours. The patients were more noisy and felt subjectively very much worse. Sometimes they felt as if they were in an oculogyric crisis: they were noisy (shouting) and flushed; and yet neither the tonic nor the nystagmoid phase was present. The crises were distinctly more prolonged; and were also of greater frequency - especially in the women. In one of them (C.Mc., Case 5) vertigo was very disabling. She was unable to sit up, and later she had the sensation that objects in the ward were continuously moving around her. In these patients swallowing was worse and very disabling. The addition of phenobarbitone 30 to 60 mg. three times daily did not give any relief. Treatment with sodium phenytoin /

phenytoin had to be discontinued after only three weeks in the case of the women patients, and there was then a striking improvement in their condition. By contrast, two male patients were able to tolerate phenytoin therapy but as they had derived no benefit from this drug it was withdrawn after a period of 12 weeks.

3. Benzhexol and Orphenadrine

The newer drugs used in the symptomatic relief of Parkinsonism, benzhexol (Artane) and orphenadrine (Disipal), do not seem to be of great value in the prophylaxis of oculogyric crises, but they seem to be of some value in preventing recurrence of sweating crises. This will be referred to in detail in Chapter 6.

SURGERY does not seem to have much place in the management of patients subject to oculogyric crises. Klemme (1941), however, reported that oculogyric crises can be eliminated by excision of the premotor cortex in the second frontal convulution just anterior to the area that produces spasmodic upward movement of the eyes on faradic stimulation. These cases however were not followed up for long periods. Motor defects on the opposite side are common complications following this operation and it is significant that this operation is now rarely performed. Cooper et al (1958) found that chemopallidectomy and chemothalamectomy have little or no effect on the occurrence of oculogyric crises. Severe sweating crises however can be abolished or greatly reduced in their severity by chemopallidectomy (Narabayashi et al., 1956). Alternatively sweating crises can be completely /

completely relieved as they occur by using parenteral injections of sodium phenobarbitone as described above. It follows that neurosurgical operations should not be performed until the effects of symptomatic medical treatment have been assessed as carefully and as objectively as possible.

SUMMARY AND CONCLUSIONS

The treatment of severe oculogyric and sweating crises in 11 patients with post-encephalitic Parkinsonism has been studied.

The value of 200 mg. sodium phenobarbitone given intramuscularly or sodium amylobarbitone 200 to 300 mg. given orally was assessed. Neither of these forms of treatment affected the natural course of crises when these were in the category classified as "severe".

A therapeutic trial was carried out to evaluate sodium phenobarbitone 150 mg. given intravenously and 50 mg. given intramuscularly in severe crises, using injections of normal saline as the control. Relief was obtained in 20 to 40 minutes after these injections of the barbiturate. Injections of normal saline were ineffective. It is suggested that in severe crises sodium phenobarbitone injected intravenously is the treatment of choice. Although parenteral injections of hyoscine hydrobromide is effective in controlling severe oculogyric crises, the use of intravenous sodium phenobarbitone is to be preferred. The use of parenteral injections of atropine sulphate is not recommended.

The prophylactic value of sodium phenytoin was determined in 5 patients suffering from severe oculogyric crises. This drug altered the character of the oculogyric crisis but did not reduce its frequency, or severity.

The writer has no experience of oculogyric crises induced by drugs /

drugs of the phenothiazine series such as Perphenazine, but there appears to be a prima facie case for the intravenous injection of sodium phenobarbitone in this type of medical emergency.

CHAPTER IV

THE ELECTROENCEPHALOGRAM IN POST-ENCEPHALITIC PARKINSONISM

INTRODUCTION

Previous electroencephalographic studies in Parkinsonism (Jasper and Andrew 1938; Schwab and Cobb 1939; Newman, McNaught and O'Donnell 1949; England, Schwab and Peterson 1959) have led to conflicting conclusions. Thus Newman and his colleagues (1949) studied 12 patients suffering from Parkinsonism (6 from arteriosclerotic and 6 from post-encephalitic Parkinsonism). They concluded that patients suffering from Parkinsonism do not show slow activity in the electroencephalogram (E.E.G.) apart from that which results from somatic tremor. Schwab and Cobb in 1949 studied 37 patients (15 suffering from post-encephalitic Parkinsonism and 22 from the arteriosclerotic type). They concluded that although head tremor can produce an artefact, this can be eliminated by restraining movement of the head; or its presence can be confirmed by recording from leads placed on the chin or on the bridge of the nose. They did not however find any significant abnormality in the E.E.G. of their patients. In a more recent study (England, Schwab and Peterson, 1959) they found that 52% of their patients showed E.E.G. abnormalities and in 21%, the E.E.G. was grossly abnormal. About half of their patients gave a history of a previous /

previous attack of encephalitis lethargica. These authors do not state whether these contrasting results were obtained from study in the same group of patients after an interval of about 20 years. If the majority of the patients in the two series were different, it must be concluded that the contrasting results were significant or that they were attributable to differences of techniques or interpretation.

One of the most disturbing sequelae of encephalitis lethargica is oculogyric crisis. Apparently no definitive study of the E.E.G. characteristics has been made in patients subject to attacks of oculogyric crisis, nor has the E.E.G. in such patients been studied during oculogyric crises. Gibbs and Gibbs (1947) however studied 240 cases of encephalitis from a variety of causes and found that in general the E.E.G. was abnormal in the acute stage. He noted that the record returned to normal with the passage of time except in patients likely to have seizures and in 17 patients with Parkinsonism, 3 patients subject to attacks of oculogyric crisis, and 24 patients suffering from narcolepsy.

In the present series there are 20 patients who periodically suffer from oculogyric crisis. It was therefore considered well worth while to study electroencephalographic records both in patients subject to attacks of oculogyric crises and those in whom there was no record of these attacks. It was also decided to obtain records of the E.E.G. in some patient during crisis, before and after treatment with intravenous sodium phenobarbitone as already described.

The /

The effect of prostigmin on the E.E.G. was also studied. It has been shown in experimental animals that 1% physostigmine applied to the cerebral cortex caused a reduction in the amplitude of the slow waves. (Miller, Stavraky and Woonton, 1940). Chatfield and Dempsy (1942) showed that prostigmin when applied as a 1% solution to the cerebral cortex in lightly anaesthetised cats produced a reduction in spontaneous activity of the cortex. Acetylcholine applied alone to a cortex which had not been pre-treated with physostigmine or prostigmin either had no effect on the cortical potentials or caused a reduction in the amplitude of the slow waves. When acetylcholine was applied to a cerebral cortex which had been pre-treated with physostigmine or prostigmin, it caused profound changes in the E.E.G. At first spontaneous bursts were augmented in size increasing both in voltage and duration, later the bursts became larger and sharper - signalled by the appearance of spikes in the record. The spikes were associated with peripheral motor effects. Brenner and Merrit (1942) showed that these effects could however be produced by using acetylcholine alone, but that very high concentrations were required and the duration of action was relatively very much shorter than when the cortex had been pre-treated with prostigmin. The results of these studies suggest that the electrical activity of the brain may be mediated through the effect of acetylcholine. Whitteridge (1948), in a review of the role of acetylcholine in synaptic transmission, concluded that the main action of acetylcholine in the nervous system seems /

seems to be the facilitation of repetitive activity, particularly in the interneurones.

In the human subject physostigmine and prostigmin have been shown to affect the electrical activity of the brain in epileptics. Williams (1941) and Williams and Russell (1941) found that in six out of nine experiments in five patients suffering from petit mal, there was a diminution of the epileptic discharges, the improvement beginning about 15 to 30 minutes after injection of physostigmine and lasting about 50 minutes on the average. With regard to prostigmin, there was a significant increase in the epileptic activity (in the 8 experiments on 4 patients with petit mal) when 1.5 mg. of the drug was injected subcutaneously. With regard to the effects of this drug on spontaneous epilepsy they found that 1 to 2 mg. of physostigmine given subcutaneously produced a reduction in the amount of spontaneous epilepsy in two patients and an increase in two other patients. Prostigmin (0.6 to 1.5 mg. subcutaneously) on the other hand produced an increase in spontaneous epilepsy. Atropine 0.6 mg. given subcutaneously reduced the number of spontaneous epileptic attacks and also reduced the amount of epileptic discharges induced by prostigmin. They also observed that the electrical changes induced by prostigmin and physostigmine were not related to the peripheral effects of these drugs, namely abdominal colic, nausea, vomiting, etc. It appears therefore that the anticholinesterases, especially prostigmin, may alter the electrical activity of the brain in patients subject to "epileptic" /

"epileptic" attacks.

During experiments designed to study the effects of prostigmin on skeletal muscular power in 7 of our post-encephalitic patients (who had appreciable muscular weakness) it was found that while 0.5 to 1 mg. of prostigmin given intramuscularly had no effect on the strength of the grip, it appeared to be capable of inducing an oculogyric crisis. Four of the 7 patients suffer from periodic attacks of oculogyric crisis; and it was observed that oculogyric crises occurred in three out of eight occasions in three of the four patients, about one hour after administering prostigmin. In view of this finding and the known effects of prostigmin in "epileptic" patients, it was decided to study the effect of intramuscular prostigmin on the electrical activity of the brain, both in patients subject to oculogyric crisis and also in those free from such attacks.

MATERIAL AND METHOD

The patients included in this study were of necessity selected, as it was essential to include only patients who suffer from milder forms of tremor in an attempt to eliminate or diminish the tremor artefact from the records. It was also desirable to include at least ten patients who were known to suffer from periodic attacks of oculogyric crisis.

Thirty patients were selected for study and their ages ranged from 38 to 63 years with an average age of 51.6 years. Thirteen of them /

them are subject to attacks of oculogyric crisis. A definite history of a previous attack of encephalitis lethargica was obtained in 27 of the 30 patients. Table 6 shows the age distribution in this series of 30 patients.

Age group in years.	20-29	30-39	40-49	50-59	60-69	70-79
No. of patients	0	1	9	17	3	0

TABLE 6: Age distribution in this series of 30 patients.

The electroencephalographic study was divided into the following parts:

1. Resting E.E.G. in the 30 patients, while they were receiving their usual medication; (10 received orphenadrine; 1 patient each received Atropine 0.6 mg. thrice daily and N-ethyl-nortropine benzhydryl ether hydrobromide (UK. 738) thrice daily; all the others were receiving benzhexol 15 to 30 mg. daily).
2. In 12 patients the resting E.E.G. was also taken when the patients had been receiving placebo therapy for 15 hours or more. The last dose of "active" tablets was given at 12 noon on the previous day and at his 6 p.m. placebo tablets were given instead. The next day (the day of the examination), placebo tablets /

tablets were again given at 8.30 a.m. and records were taken, some time between 9.30 a.m. and 4 p.m.

3. Records of the E.E.G. were obtained from three patients during oculogyric crisis and the effect of 0.2 mg. of sodium phenobarbitone given intravenously was studied. The E.E.G. was taken on one or more occasions between 20 to 60 minutes after giving the sodium phenobarbitone. Owing to technical difficulties already mentioned in the preface, it was not possible to study more patients.

4. The effect of parenteral prostigmin on the E.E.G. was studied in 12 patients, 8 of whom suffer from oculogyric crisis. On the previous day, placebo tablets were substituted for the night dose of the drug normally taken by the patient for Parkinsonism, and again on the morning of the test, placebo tablets were given. Prostigmin 1.5 mg. was given intramuscularly into the upper lateral quadrant of the gluteal region and the area was massaged for one minute. E.E.G. was recorded 15, 30 and 60 minutes after giving the injection and this was compared with the electroencephalogram taken before the administration of prostigmin. Any peripheral effects of the drugs, namely flushing of the skin (face), sweating, change in heart rate, salivation and abdominal colic were recorded.

When abnormal waves were seen in the record the effect of holding

the /

the head absolutely steady was noted. By this means it was possible to detect if the abnormal waves were due to movement artefacts.

An Offner Type T Transistor Portable Electroencephalograph (8 channels) was used. The electrodes were normal silver-chlorided type fixed to scalp by harness. Recordings were made in para-sagital and para-coronal planes (positions I and II respectively).

RESULTS

1. The resting E.E.G.s of the 30 patients while receiving their usual treatment.

The E.E.G.s were considered to be frankly abnormal in nine patients (30%). A very common finding was theta activity which was diffuse but usually more prominent in the frontal areas (66%). In addition to theta activity, four patients had frontal delta waves.

The E.E.G.s were divided into four types:

Type 1. Eight patients had records of this type. The records were normal according to standard criteria and had sustained alpha activity and a minimum voltage of 40 μv. They showed a normal response to opening the eyes. (Fig.15). Two patients suffer from oculogyric crises.

Type 2. Five patients had records of this type. The E.E.G.s were similar to Type 1 except that bursts of theta activity greater than 40 μv. were present (Figures 16 and 19a). All these records were therefore abnormal.

One /

One patient suffers from oculogyric crisis and one from breath-holding attacks.

Type 3. Twelve patients had this type of record. The records were of low voltage, between 25 μv. and 35 μv. (Fig. 17). Alpha activity was present but was not well sustained. It was inhibited by opening the eyes. Five patients are subject to attacks of oculogyric crisis.

Type 4. Five patients had this type of record. The records were of very low voltage, between 10 μv. and 20 μv., and opening the eyes produced no change (Fig. 18). All the patients are subject to attacks of oculogyric crisis.

2. The alpha rhythm.

Twenty-eight of the 30 patients were considered to have definite alpha rhythm although in some cases because of the very low voltage it was very difficult to identify the waves. As already stated, in only 13 patients was the magnitude of the alpha waves up to 40 μv. The average frequency of the alpha waves was 9.7 cycles per second and 20 of the 30 patients had waves between 9 and 11 cycles per second (Table 7). An interesting feature was the fact that there was a well sustained alpha rhythm in only 12 of the 30 patients (40%). The other 18 patients (60%) had poorly sustained alpha rhythms showing a poor response to opening and closing of the eyes.

Frequency of alpha waves (Cycles per sec.)	7	8	9	10	11	12
No. of patients	2	3	6	9	5	3

Mean Frequency = 9.7 cycles per second

TABLE 7: Distribution of alpha waves between 7 and 12 cycles per second

3. Effect of Anti-Parkinsonian drugs on the E.E.G.

In 12 patients withdrawing active drug therapy for 15 or more hours had no significant effect on the E.E.G.

4. Effect of age on the E.E.G.

Age appeared to have no effect on the normality of the E.E.G.; the average age of the 9 patients with abnormal records was 53.7 years and that for the patients with normal records was 50.6 years. Age also appeared to have no effect on the voltage of the electroencephalogram. Thus the average age of the 13 patients having "normal" voltage records was 52.4 years while the average age for the 17 patients with low voltage records was 50.9 years.

5. Relationship between the type of E.E.G. and susceptibility to attacks of oculogyric crisis

From Table 8 it will be seen that of the 13 patients who suffer from periodic attacks of oculogyric crisis, 10 had low voltage activity and in 5 of them the voltage of the alpha rhythm when the eyes /

Type of E.E.G.	No. of patients with oculogyric crisis	No. of patients without oculogyric crisis	Total No. of patients.
Type I. Alpha > 35 µv.	2	6	8
Type II Theta and Alpha > 35 µv.	1	4	5
Type III Alpha 25 - 35 µv.	5	7	12
Type IV. Alpha 10 - 20 µv.	5	0	5

TABLE 8. Relationship between the type of E.E.G. and susceptibility to attacks of oculogyric crisis.

Type of E.E.G.	No. of bedfast patients	No. of ambulant patients	No. of patients with severe or moderate rigidity.	No. of patients with mild rigidity.
Type I. Alpha > 35 µv.	3	5	6	7
Type II Theta and alpha > 35 µv.	2	3		
Type III Alpha 25-35 µv.	8	4	14	3
Type IV Alpha 10-20 µv.	3	2		

TABLE 9. Relationship between type of E.E.G., state of ambulation and degree of rigidity.

eyes were closed was 20 μv. or less. In contrast, only 7 of the 17 patients who do not suffer from oculogyric crisis had low voltage records. It was also of interest that there were no patients in the very low voltage group who did not have oculogyric crisis. Low voltage tracings are therefore much more commonly seen amongst patients subject to oculogyric crisis.

6. Effect of state of ambulation on the voltage of the electroencephalogram.

16 of the 30 patients were non-ambulant and 14 patients were ambulant. It was of interest that 68.7% of the 18 non-ambulant patients were in the group having low voltage potentials (Types III and IV). In contrast, only 6 of the 14 ambulant patients (42.8%) had low voltage tracings. It therefore appeared that low voltage tracings were more commonly seen in non-ambulant patients and in patients subject to oculogyric crisis. Table 9 gives the details. More will be said of this later in the discussion.

7. Effect of severity of rigidity on the voltage of the electroencephalogram

Some correlation also appeared to exist between the severity of rigidity and the voltage of the E.E.G. Thus 14 out of 20 patients with rigidity classed as moderate or severe, had low voltage tracings whilst only 3 out of the 10 patients whose rigid state was classed as mild (+) had low voltage tracing (Table 9).

8. Effect of the state of ambulation on the normality of the E.E.G.

The /

The E.E.G.s were considered to be frankly abnormal in 9 patients, three of which were obtained from the 14 ambulant patients and 6 from the 16 non-ambulant patients. The ratio of abnormal E.E.G.s in ambulant and non-ambulant patients was therefore 4.3 : 7.5, but the expected ratio should be 7 : 8. The incidence of abnormal E.E.G.s in non-ambulant patients therefore appears to be about double that in ambulant patients. However, in view of the fact that the total number of abnormal records is small, no valid general conclusion may be drawn.

9. E.E.G. during oculogyric crisis

Three patients subject to periodic attacks of oculogyric crisis were studied when they were in oculogyric crises. Two of these patients when not in crisis had E.E.G. of voltage potential above 50 μv.

Three points of interest were observed in the E.E.G. of these patients when they were in oculogyric crisis:

(a) The voltage of the electroencephalogram during oculogyric crisis became very low and this was more noticeable in the two patients whose records were otherwise of high voltage. Figs. 19 a, b, and c show the E.E.G. in one of the latter patients before, during and after an oculogyric crisis.

(b) The three patients showed high voltage spikes in the anterior areas. The significance of this will be discussed later. These spikes disappeared when intravenous sodium phenobarbitone controlled the oculogyric crisis (Figs. 19 and 20).

(c) /

(c) The alpha rhythm increased in rate in two of the three patients and in one of them prominent beta activity was seen before the administration of sodium phenobarbitone intravenously. During the 40 to 60 minutes following this injection, the beta activity usually became the dominant rhythm.

Effect of prostigmin on the E.E.G.

Out of the 12 patients who received 1.5 mg. of prostigmin intramuscularly, 4 showed a slight increase in the amplitude of the electrical potentials, and in two patients slower rhythms were induced. Thus one patient (H.Dev.) before the injection of prostigmin had a low voltage record with the dominant alpha activity at 9 cycles per second. Scattered theta waves at 6 cycles per second were also present. Fifteen minutes after the injection the voltage was slightly higher and the dominant rhythm was now 6 to 7 cycles per second but with frequent outbursts of activity at 4 to 5 cycles per second.

Oculogyric crises were not induced in the 8 patients subject to such attacks although peripheral manifestations of parenteral administration of prostigmin were conspicuous in the present series of patients. Thus there was increased secretion of saliva in 10 of the 12 patients, definite flushing of the face was seen in 6 patients, sweating in 4 patients, and there was appreciable slowing of the heart in 10 patients. Two patients however complained of abdominal pain (colic) and one of them required treatment with atropine sulphate (0.6 mg. subcutaneously). These disturbances and the changes in the E.E.G. occurred from 15 to 30 minutes after injecting prostigmine.

(a).

Fig. 15. E.E.G. Type I (alpha > 35 μv.).

J. McC. Male, aged 51 years. Encephalitis lethargica 1925. Ambulant. Moderate degree of rigidity. Tremor mild.

E.E.G. 4.8.60. Normal voltage record. Well sustained alpha rhythm - 11 cycles per second. Normal physiological response.

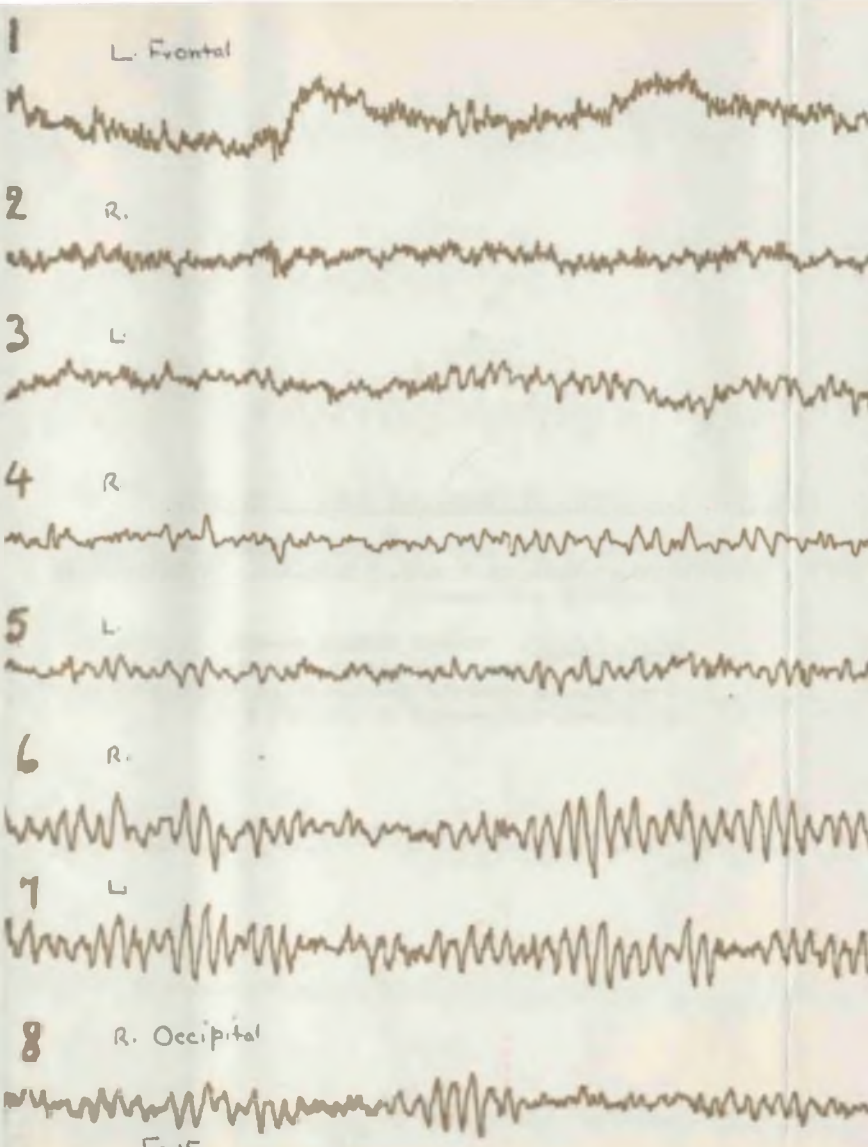
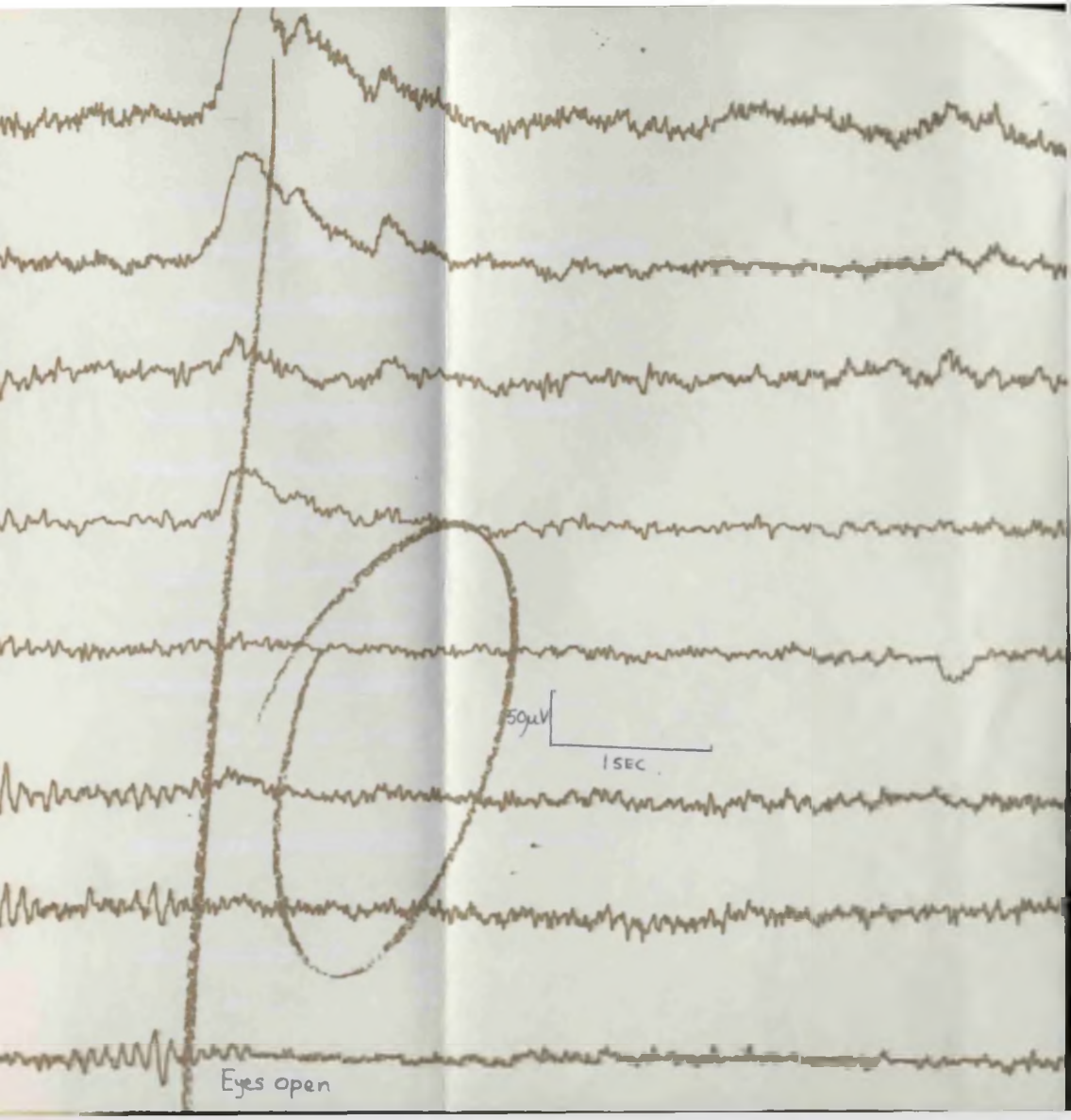


Fig. 15


50μV
1 SEC
Eyes open

(b)

Fig. 16. E.E.G. Type II (theta and alpha > 35 µv.).

M. Aus. Woman aged 59 years. History of encephalitis lethargica ? date. Ambulant. Mild degrees of rigidity and tremor.

E.E.G. 5.5.60. Normal voltage record. Dominant rhythm at 10 cycles per second, interspersed with short runs of abnormal frontal delta rhythm (3 cycles per second) more marked on the left side.

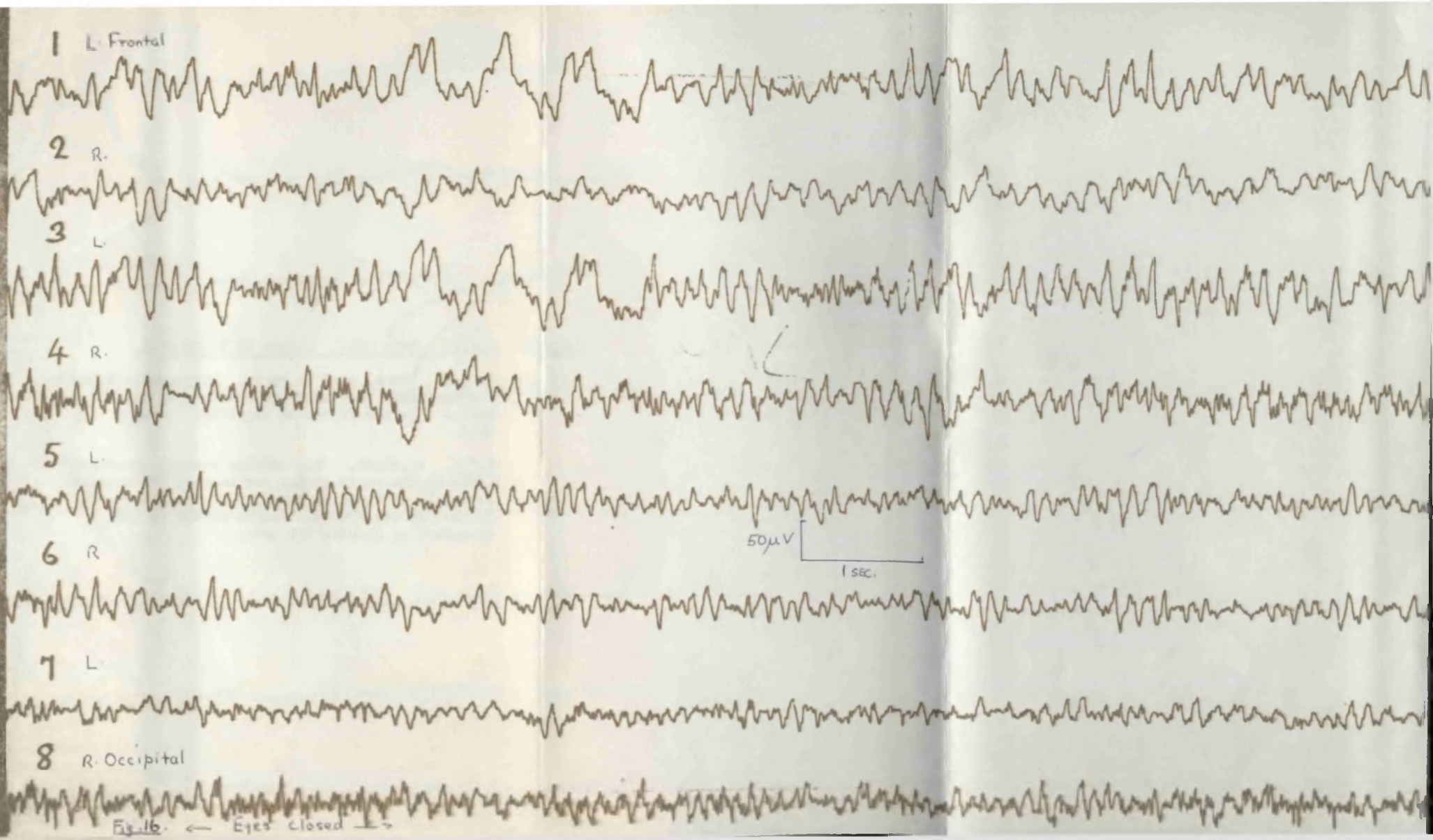


Fig. 16. ← Eyes closed →

(o).

Fig. 17. E.E.G. Type III. (Alpha 25 to 35 μv.).

J. Esp. Male, aged 51 years. Encephalitis lethargica 1927. Non-ambulant but able to sit in chair. Severe degree of rigidity. Tremor very mild.

E.E.G. 14.12.60. Low voltage record. Dominant alpha rhythm at 10 cycles per second. Occasional outbursts of theta rhythm at 7 cycles per second in the frontal region. Alpha rhythm is ill-sustained on closing the eyes.

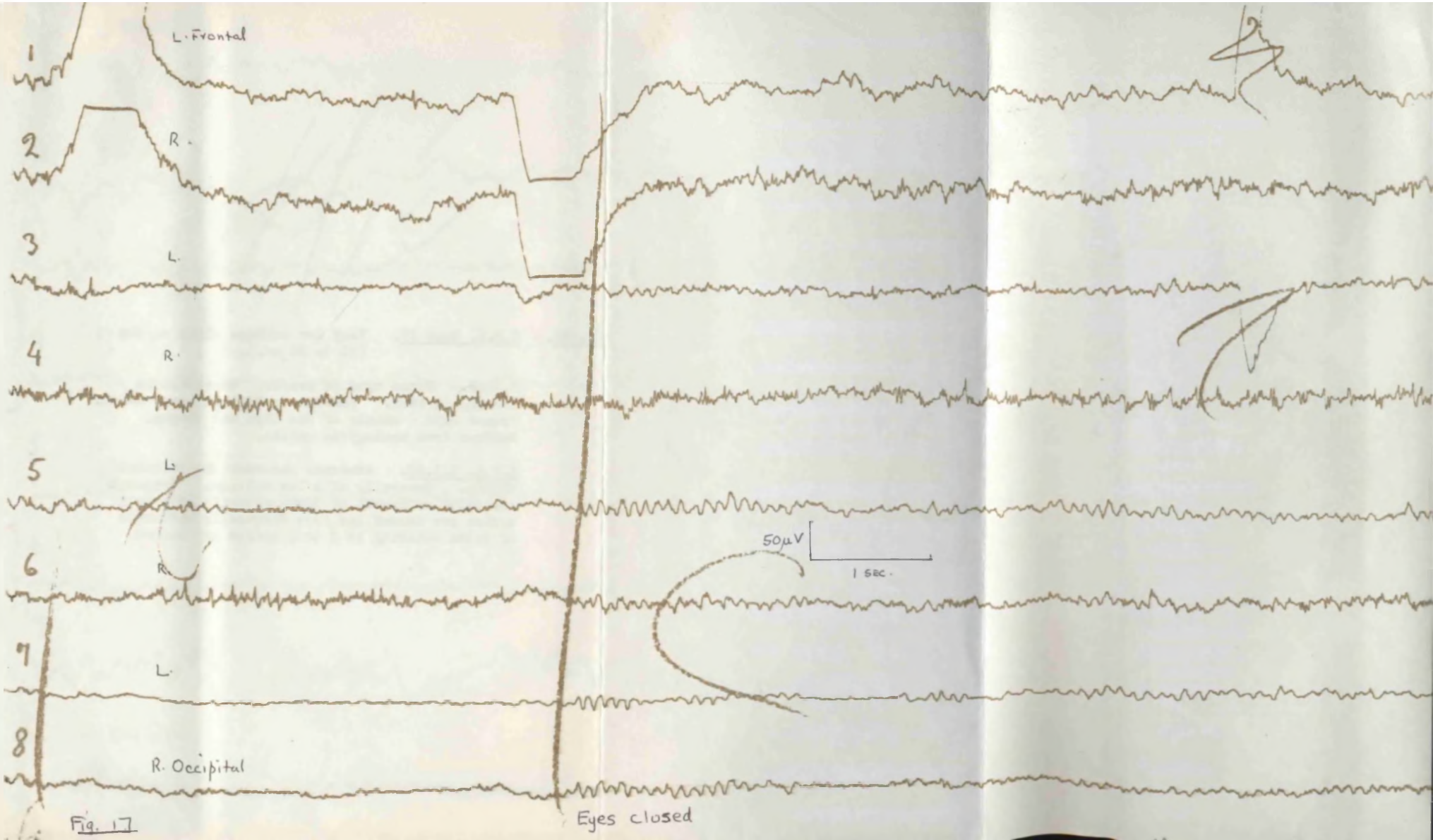

1
L. Frontal
2
R.
3
L.
4
R.
5
L.
6
R.
7
L.
8
R. Occipital
50μV
1 sec.
Eyes closed

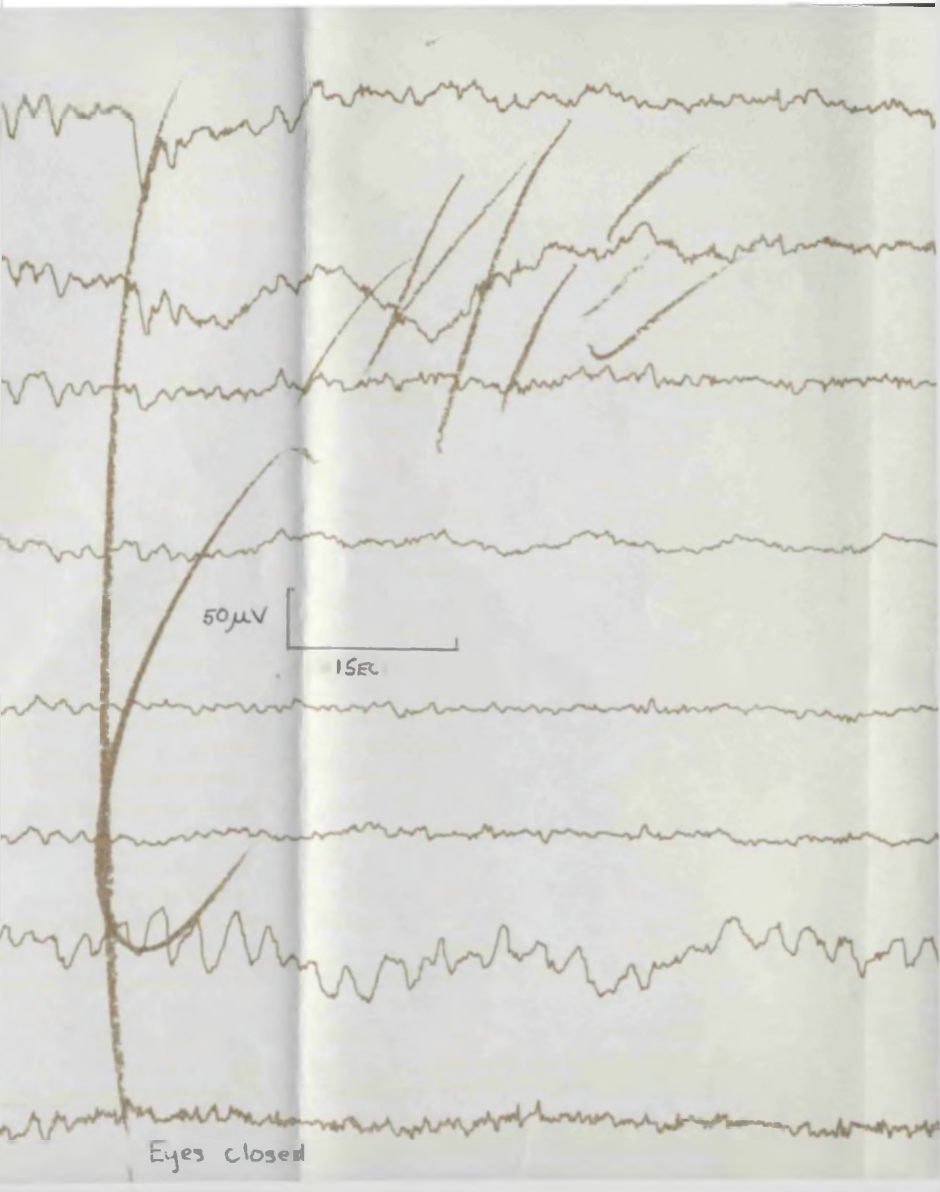
Fig. 17

(d)

Fig. 18. E.E.G. Type IV. Very low voltage alpha rhythm (10 to 20 μv.).

C. McK. Woman aged 57 years. Encephalitis lethargica 1924. Bedfast. Rigidity very severe. Tremor mild - mainly of the lips and tongue. Suffers from oculogyric crisis.

E.E.G. 5.5.60. Abnormal record. No dominant rhythm. Generally of a low voltage. Frequent scattered outbursts of theta activity at 6 to 8 cycles per second and less frequently outbursts of delta activity at 3 to 4 cycles per second.


50μV
1SEC
Eyes closed

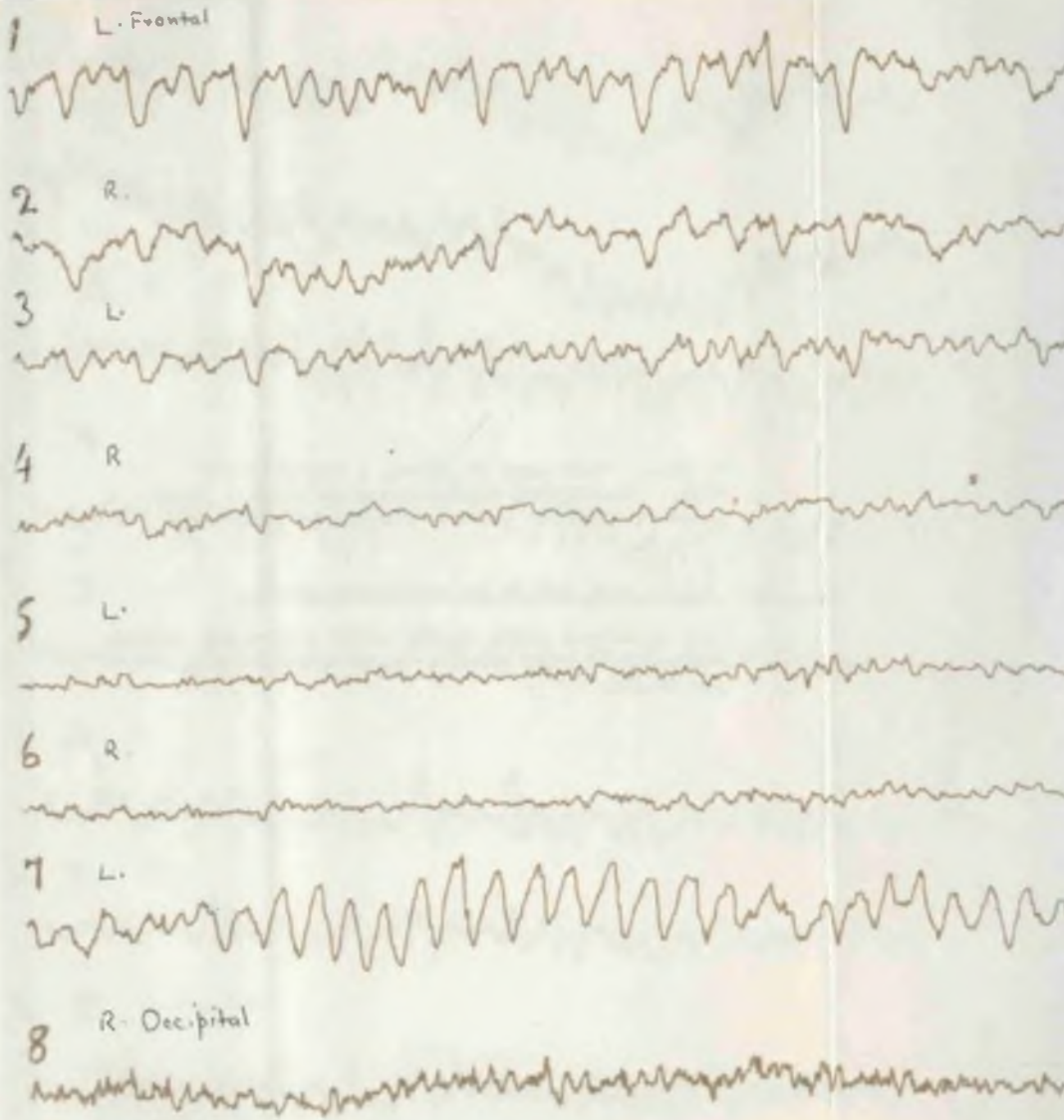


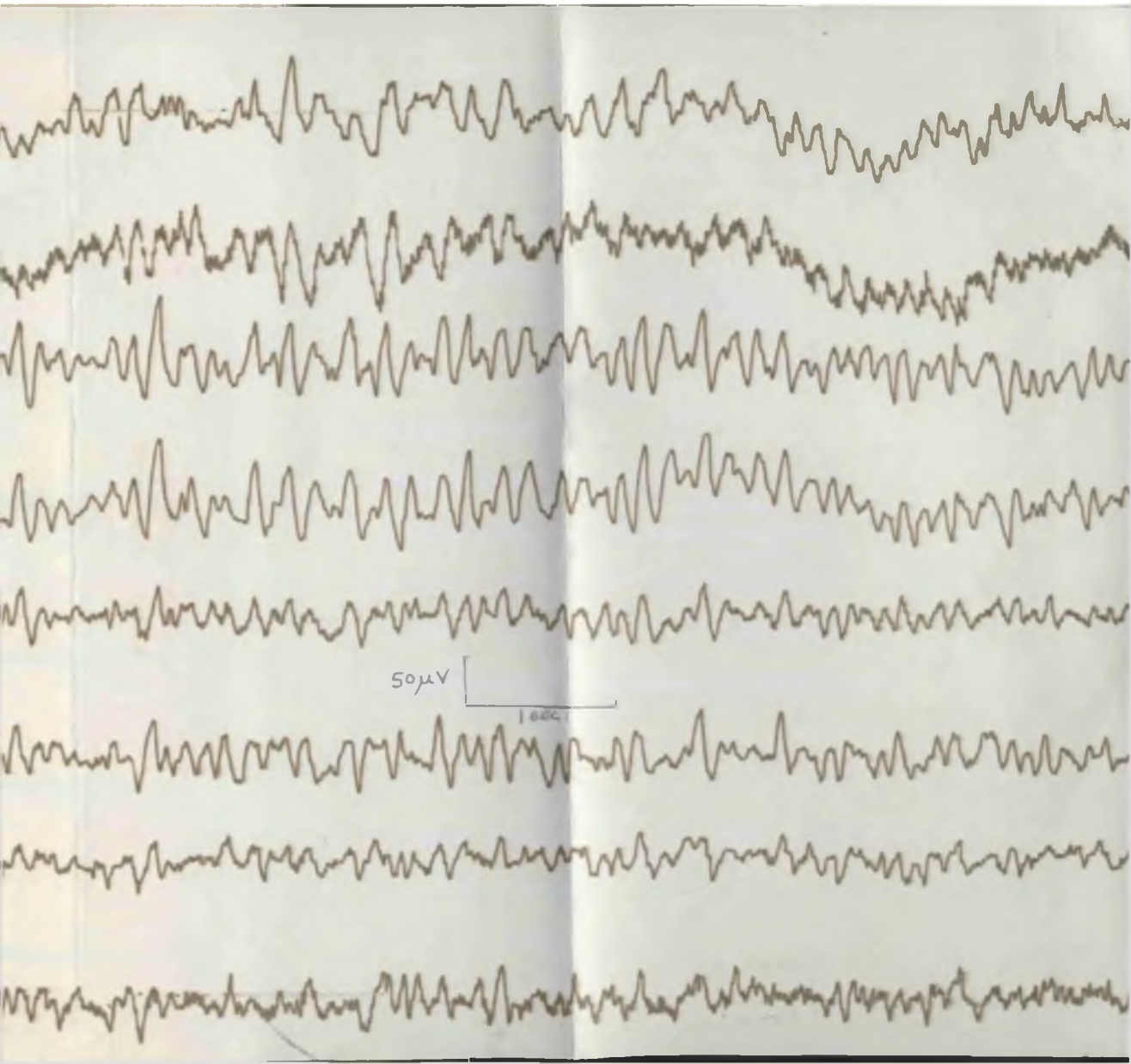
Fig. 18

(e)

W. Sha. Male aged 54 years. Encephalitis 1921. Oculogyric crises began in 1938. Blood pressure 130/80. Heart rate 80 per minute.

Fig. 19a. E.E.G. when not in an oculogyric crisis.

Well sustained alpha rhythm at 10 cycles per second. Outbursts of high voltage theta activity at 6 cycles per second.


50μV
1 sec.

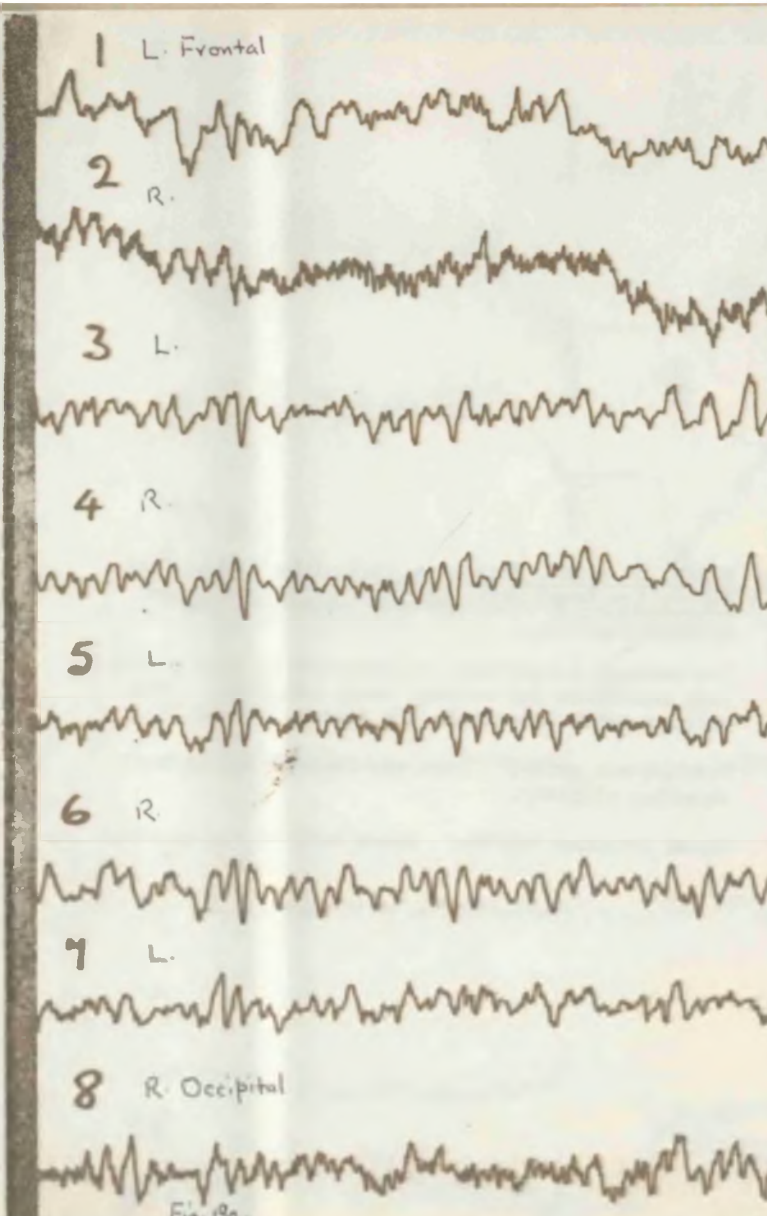


Fig. 18a.

(f).

Fig. 19b. E.E.G. of W.Sha. during an oculogyric crisis, but before treatment with intravenous sodium phenobarbitone (0.2g.).

Low voltage potentials, ill-sustained alpha rhythm with scattered low voltage theta activity. High voltage spike potentials are present frontally.

Patient was noisy. Face was flushed and he was sweating slightly.

Blood pressure 150/80. Heart rate 96 per minute.

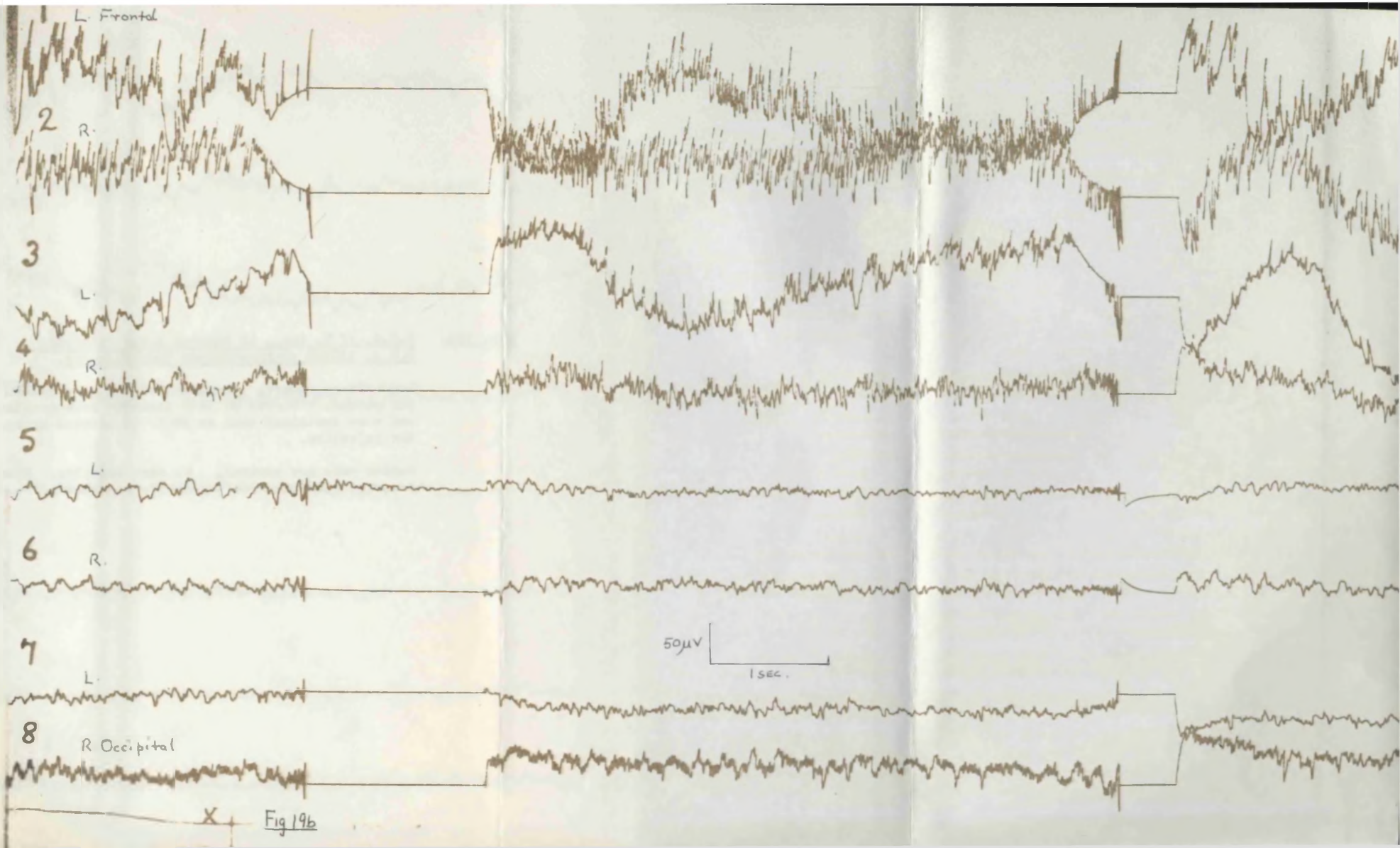


Fig 19b

(8).

Fig. 19c. E.E.G. of W. Sha., 40 minutes after receiving 0.2 g. sodium phenobarbitone intravenously.

Low voltage record. Dominant rhythm at 6 cycles per second. Bursts of beta activity more prominent and more sustained than at 20 or 30 minutes after the injection.

Ocular axis now central. No more sweating. Blood pressure 134/80. Heart rate 86 per minute.

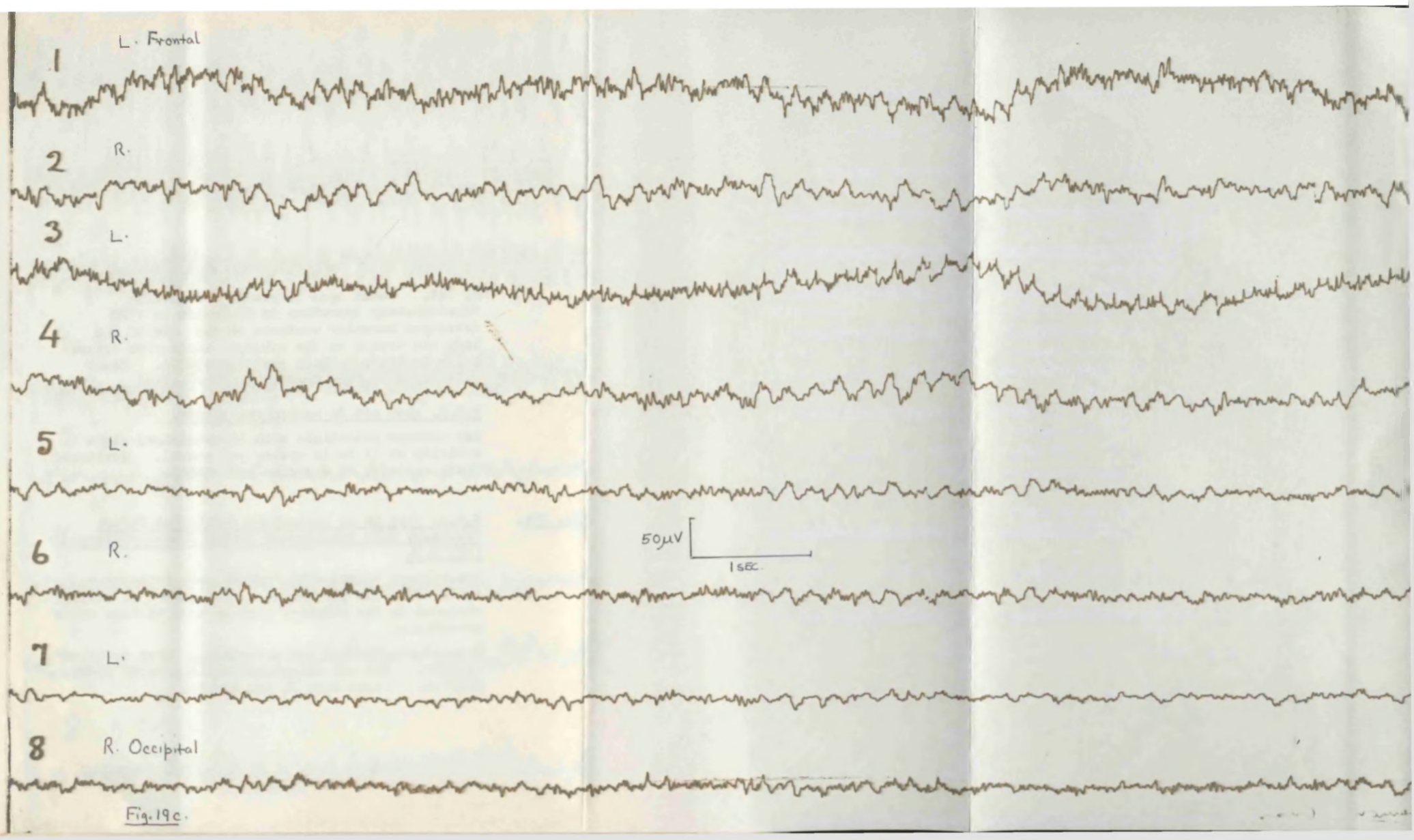


Fig. 19c.

J. Pat. Woman aged 57 years. Following tonsillectomy operation in Australia in 1928 developed muscular weakness on one side of the body and tremor on the other. Oculogyric crises began in 1942. Blood pressure 170/90. Heart rate 70 to 80 per minute.

E.E.G. when not in oculogyric crisis.

Low voltage potentials with ill-sustained alpha activity at 11 to 12 cycles per second. Scattered theta activity at 6 cycles per second.

Fig. 20a. E.E.G. when in an oculogyric crisis but before treatment with intravenous sodium phenobarbitone (0.2 g.).

Low voltage record with runs of beta activity - 18 to 20 cycles per second. The record is largely obscured in the anterior part by high voltage spike potentials.

Patient was flushed and was noisy. Eyes deviated upwards. She had slight epistaxis. Blood pressure 210/116. Heart rate 74 per minute.

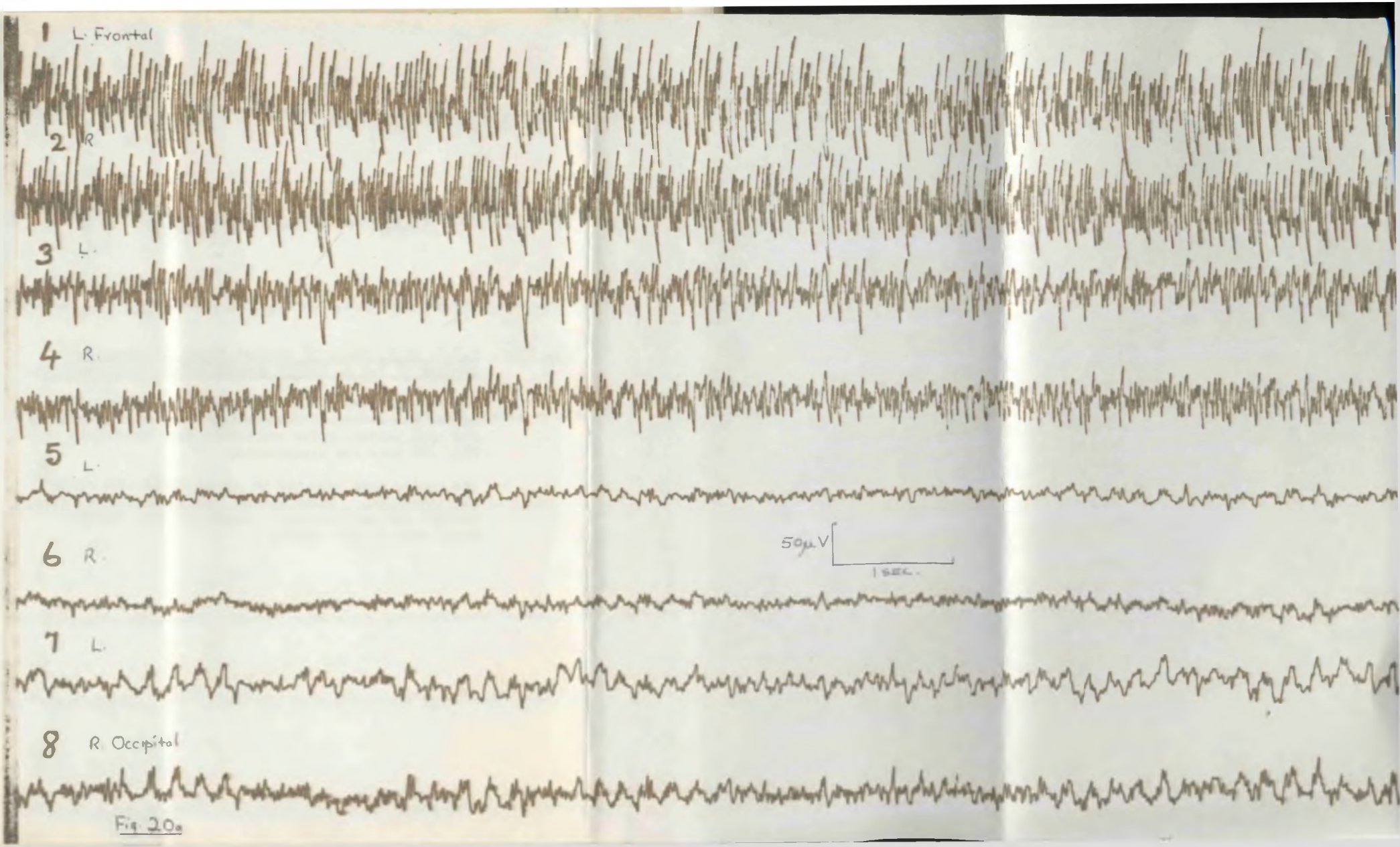


Fig. 20a

(i).

Fig. 20b. E.E.G. of J. Pat., 30 minutes after the administration of 0.2 g. sodium phenobarbitone intravenously.

Low voltage record with dominant alpha rhythm at 12 cycles per second. Beta activity now more prominent. The high voltage spike potentials seen anteriorly in Fig. 20a have now disappeared.

The ocular axes returned to normal 20 minutes after the injection. There was no more epistaxis and the patient was now smiling. Blood pressure 160/70. Heart rate 72 per minute.

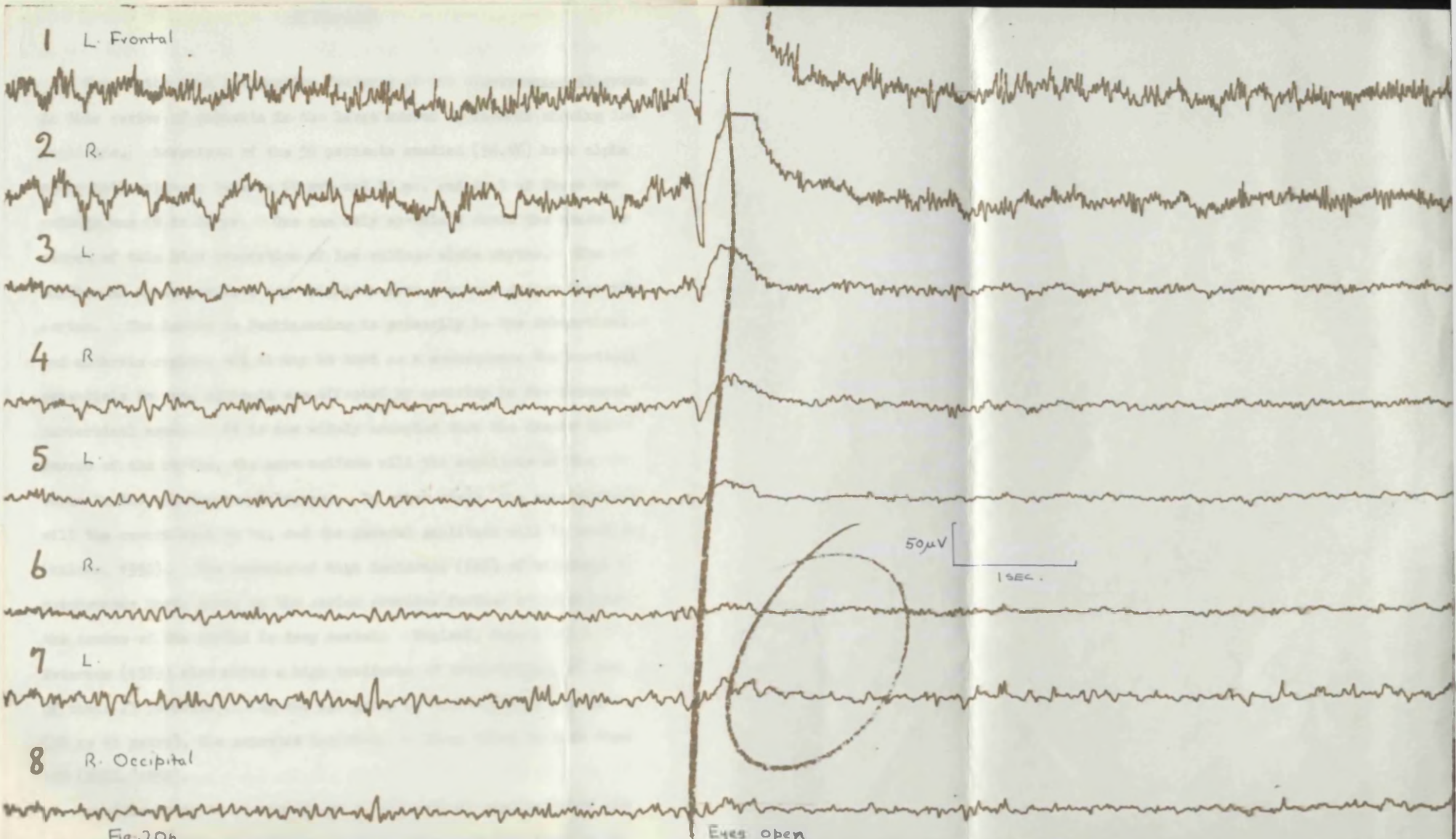


Fig 20b

DISCUSSION

One of the most interesting features of the electroencephalograms in this series of patients is the large number of records showing low amplitude. Seventeen of the 30 patients studied (56.6%) have alpha waves with voltages between 10 μv. and 35 μv. and in 5 of these the voltage was 10 to 20 μv. One can only speculate about the cause or causes of this high proportion of low voltage alpha rhythm. The rhythms in these patients may originate from a source deeper than the cortex. The lesion in Parkinsonism is primarily in the subcortical and midbrain regions and it may be that as a consequence the cortical potentials in some patients are affected by activity in the deranged subcortical areas. It is now widely accepted that the deeper the source of the rhythm, the more uniform will the amplitude of the waves in the electroencephalogram. In other words, the more diffuse will the record seem to be, and the general amplitude will be smaller. (Walter, 1950). The associated high incidence (66%) of bilaterally synchronous theta waves in the series provides further evidence that the source of the rhythm is deep seated. England, Schwab and Peterson (1959) also noted a high incidence of theta waves (52% out of their 75 patients). In the age group of the patients studied (38 to 63 years), the expected incidence of theta waves is less than 11% (Hill, 1952).

Another point to be considered is the general similarity of the electroencephalogram of patients in this series and that seen in the aged /

aged (people over 65 years of age). In those over 65 there is a general lowering of the voltage and a rather high incidence of theta waves (Obrist, 1954). This raises the question: in post-encephalitic Parkinsonism - and perhaps paralysis agitans and arteriosclerotic Parkinsonism - is there a premature aging process in the brain? Critchley (1955) made the point that although neurohistologists are not altogether convinced that a premature aging process in certain neuronic systems of the brain is a cause of Parkinsonism, the concept is an attractive one.

It is noteworthy that low voltage electroencephalograms are common in schizophrenia (Lemere, 1936 and 1938), a condition in which there are somatic manifestations not unlike those seen in severe Parkinsonism. The possibility of a relationship between the low-amplitude electroencephalogram and the occurrence of a schizoid personality was however not studied in this series.

Low amplitude electroencephalograms are more commonly seen in patients subject to attacks of oculogyric crisis, in patients with more severe degrees of rigidity and in bed-fast patients. This raises the question: is there a positive association between susceptibility to attacks of oculogyric crisis, severe rigidity and inability to walk? In Chapter V (the section which deals with deformities in Parkinsonism) it was noted that severe degrees of rigidity predisposes a patient to a bed-fast state. In other words the bed-fast state and a severe degree of rigidity are likely to be seen /

seen in the same patient. In this series, no similar relationship was observed between (a) liability to oculogyric crises and (b) the presence of gross degree of rigidity. In the 30 patients included in this electroencephalographic study, 13 of them suffer from oculogyric crises, 4 of whom have rigidity classified as mild. Seventeen patients do not suffer from oculogyric crises and 6 of them have mild rigidity. In the series as a whole (67 patients), out of the 20 patients subject to oculogyric crises 5 have mild rigidity while 11 of the 47 patients who do not suffer from oculogyric crises have mild rigidity (see Tables 3 and 4, p. 87 and 88, Chapter II).

The electroencephalogram during an oculogyric crisis is of great interest. Even in patients with a normal voltage record (that is 40 μv or over) during the inter-crises period, the E.E.G. during an oculogyric crisis is of low voltage; the alpha rate is increased and beta activity may become more obvious. Although this change in the electroencephalogram may be due to severe emotional stress which often accompanies an oculogyric crisis, the change can be explained in electrophysiological terms as being probably due to stimulation of the reticular formation. Stimulation of the reticular formation in experimental animals has been shown to lead to desynchronisation of the cortical potentials; in other words it produces a low voltage fast activity (Starzyl, Taylor and Magoun, 1951; French, Amerongen and Magoun, 1952). In Chapter II, the pathogenesis of the oculogyric crisis was discussed and from clinico-physiological considerations it was /

was considered that stimulation of the reticular formation might occur during such crises from vestibular stimulation. The findings from this electroencephalographic study appears to support this hypothesis. The high voltage spike potentials seen in the electroencephalograms in the anterior leads when patients were in oculogyric crises were considered to be muscle spike potentials. The muscle spike potentials were probably due to the tonic contraction of the extrinsic ocular muscles. It was noted that these spike potentials disappeared when the ocular axis returned to normal under the influence of intravenous sodium phenobarbitone therapy. This finding assumes considerable importance when it is considered in relation to Hall's theory (Hall, 1931) that the extrinsic ocular muscles are in a state of relaxation during an oculogyric crisis, and that the crises are due to a sleep mechanism. On the basis of purely clinical considerations, it was shown in Chapter II that this theory is untenable. The E.E.G. findings support the views detailed earlier in this Thesis and are at variance with Hall's theory.

Thirty per cent of the patients in this series were considered to have abnormal electroencephalograms because of the presence of bursts of high voltage, theta activity and delta activity. These abnormal waves were more prominent in the frontal region. England, Schwab and Peterson (1959) however found that in their series, the abnormal theta and delta waves were more prominent posteriorly. Jasper and Andrews (1938) found that in severe cases of Parkinsonism an abnormal rhythm of /

of 4 to 5 cycles per second would appear periodically. In the present series it was found that the incidence of abnormal E.E.G.s in patients with more severe degrees of rigidity was about double that in patients with mild degrees of rigidity. England, Schwab and Peterson (1959) made the point that akinesia of Parkinsonism is related to rigidity. They also found the E.E.G. in patients showing manifestations of akinesia was usually abnormal. The source or cause of the delta rhythms is unknown, but they are not associated with epileptic activity or with narcolepsy.

SUMMARY

Electroencephalographic study of 30 patients suffering from post-encephalitic Parkinsonism showed that over half of them have low voltage alpha rhythms (below 40 μv.). It would appear that in post-encephalitic Parkinsonism the phenomenon of low voltage E.E.G.s is most frequently seen in patients who are known to be liable to oculogyric crises and in those who suffer from severe rigidity and who are incidentally often bedfast.

There was a very high incidence of theta activity most prominent frontally. The records of 9 patients were regarded as definitely abnormal because of the presence of high voltage theta and delta activity. Abnormal records were more common in patients who suffer from severe rigidity.

The E.E.G. during an oculogyric crisis has the following characteristics: anteriorly there are high voltage spike potentials, in the other areas there is a general lowering of voltage, beta activity may become more obvious.

Administration of 1.5 mg. of prostigmin intramuscularly had little or no effect on the E.E.G.

CHAPTER V.

DEFORMITIES IN POST-ENCEPHALITIC PARKINSONISM

Apart from the general attitude of flexion and the main d'accoucheur deformity, deformities in Parkinsonism have received very little attention. Even Denny-Brown in his monograph on the diseases of the basal ganglia (Denny-Brown, 1946) did not lay much stress on problems arising out of deformities. However in his more recent exposition on Parkinsonism (Denny-Brown, 1960), he made some further comment on this problem, but no detailed study was reported. Schmörl and Junghanns (1959) in their monograph "Human Spine in Health and Disease", made only a passing reference to post-encephalitic Parkinsonism as a cause of spinal deformities.

Even a casual visitor to the post-encephalitic wards at Stobhill General Hospital would immediately note the variety of deformities exhibited by these patients. Not unnaturally it was decided to include in the present study of Parkinsonism a survey of these deformities and to try to gather useful information regarding their classification, pathogenesis and management. It was soon obvious that this subject - though of secondary importance in the sence that it deals with mechanical sequelae - has wide ramifications into medicine and surgery: only one or two facets of the problem are discussed in this section of the thesis. However, in view of the scantiness /

scantiness of the literature on this subject, this limited examination may provide a starting point for a more elaborate study by anatomists and orthopaedic surgeons.

Sixty-seven patients were studied. Their ages ranged from 39 to 78 years. Attention was mainly devoted to the deformities of the hands and the spine. The patients were divided into three groups -

1. Group A - 33 in number and is made up of ambulant patients.
2. Group B - Consists of non-ambulant patients who are able to sit in chairs for a few hours. There were 21 patients in this group.
3. Group C - 13 patients who are completely bedfast.

Table 12 gives the sex distribution in each group.

Deformities of the Hands

Three main types of deformities were found and have been classified as Types I, II and III.

Type I deformity

In this type of deformity there is flexion at the metacarpo-phalangeal joints, hyperextension at both the proximal and distal interphalangeal joints (Fig. 21a). The thumb is usually opposed and adducted and in one patient the pull of the adductor pollicis on the head of the metacarpal bone of the thumb was so great that the metacarpo-phalangeal joint of the thumb appeared to be subluxated (Fig. 21b). X-ray of the joint, however, revealed no abnormality of the joint. The wrist may be central, flexed or extended. Ulnar deviation /

Fig. 21a. Right hand - normal.
Left hand - Type I deformity. Note the marked adduction deformity of the left thumb.

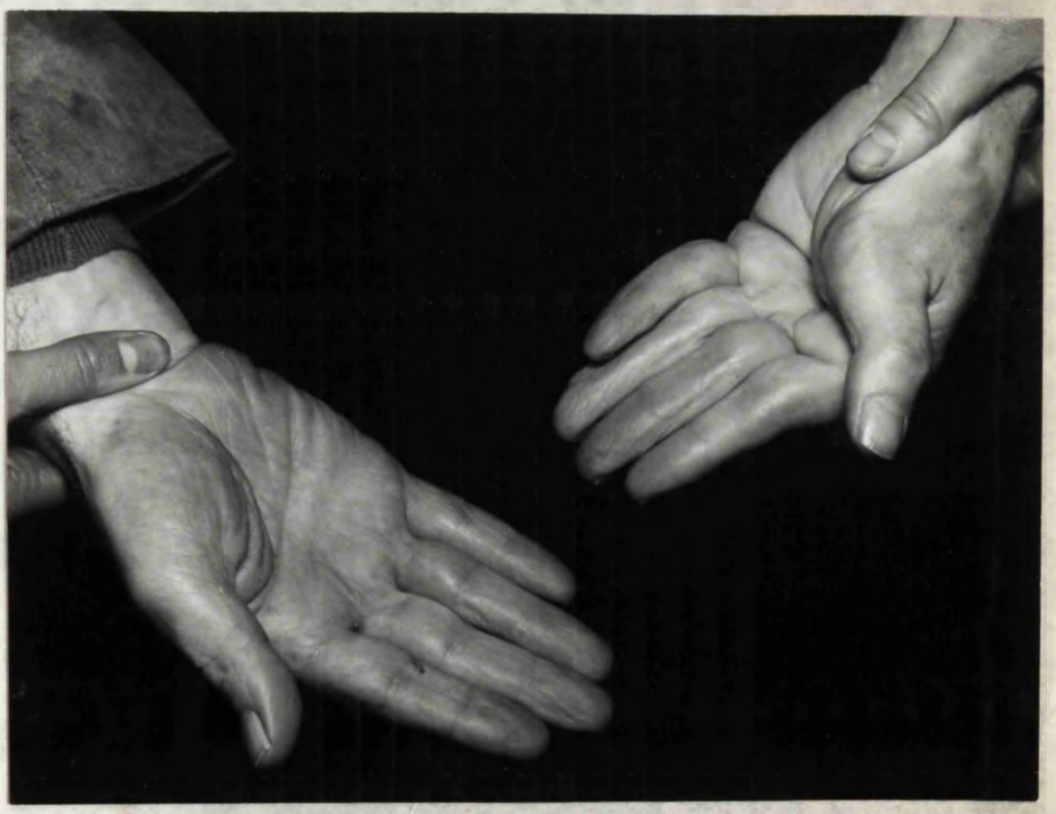


Fig. 21b. Palmar aspect of the hands in Fig. 21a. Note the gross degree of hyperextension of the proximal interphalangeal joints of the left hand.

deviation of the wrist and fingers is frequently present. There is some limitation of active adduction and abduction movements of the fingers (Fig. 22); in some patients practically no such movements are possible. Wrist movements are often limited: if the joint is flexion deformity, extension movement is more limited and vice versa if there is extension deformity of the joint.

Type II deformity

In this type of deformity the metacarpophalangeal and interphalangeal joints are flexed. The wrist is also usually flexed, although extension of the wrist is sometimes seen. The thumb is usually adducted and opposed: this may be to such a degree that the thumb protrudes either between the index and middle fingers or between the middle and ring fingers (Fig. 23). The interphalangeal joint of the thumb does not show any constant deformity: it is frequently normal but it may be flexed. Ulnar deviation of the fingers and the wrist is present in nearly 50% of cases, (15 out of 35 hands examined). The active movements of adduction and abduction of the finger are either absent or minimal.

Type IIa

A subgroup of Type II deformity can be made out. It has essentially the same features as Type II deformity proper, except that there is hyperextension at the distal interphalangeal joints, usually of the second, third and fourth fingers but sometimes of the fifth finger also (Fig. 24).

Type /

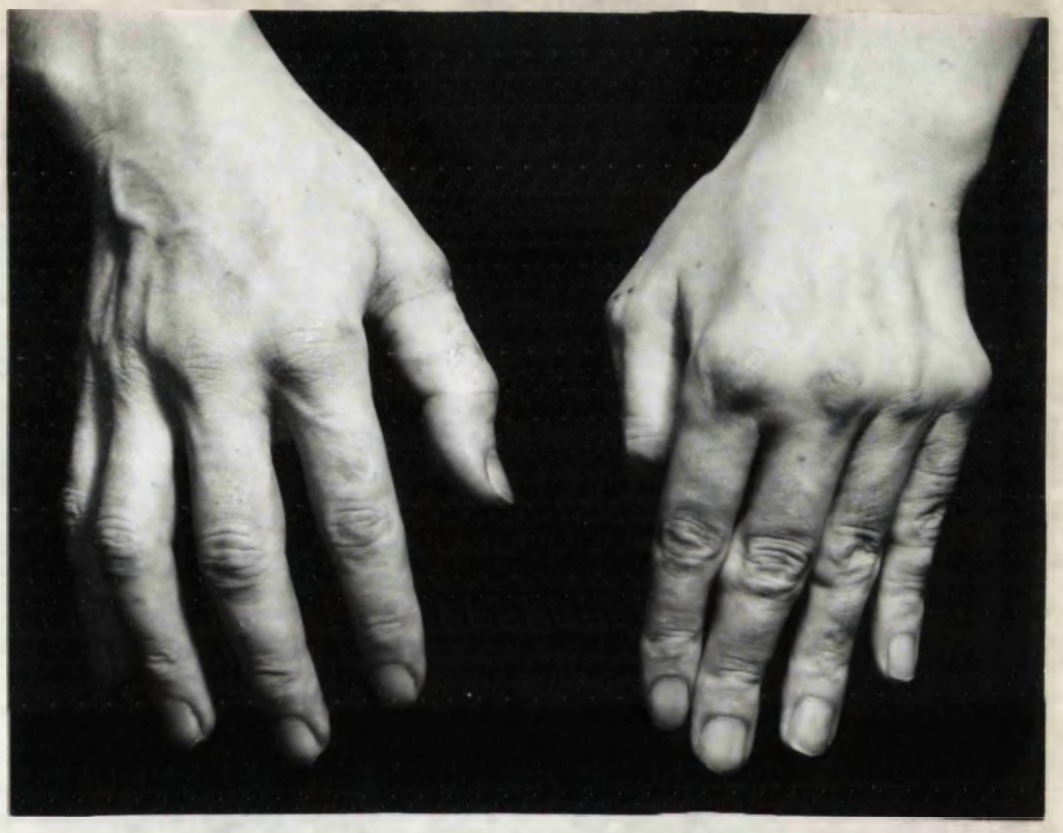


Fig. 22. Right hand - normal.
Left hand - Type I deformity.
Note absence of active abduction movement of the fingers in the deformed hand.

Fig. 23. Type II deformity. Right hand also shows gross degree of opposition deformity of the thumb.

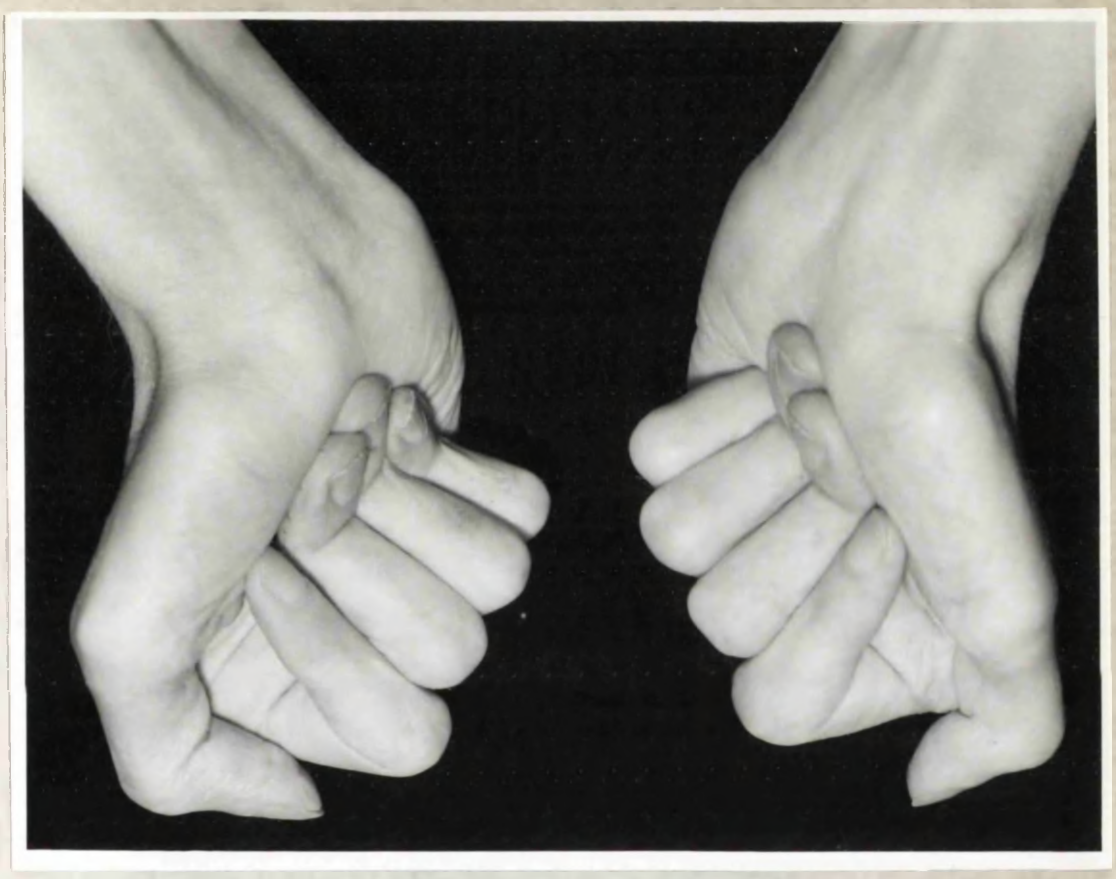


Fig. 24. Type IIa deformity.

Type III deformity (Figs. 25 a and b).

This is a very rare deformity. It was seen in only three hands (in two patients) and both were female patients.

In this type of deformity the hand resembles the "claw hand" deformity of ulnar nerve paralysis. The metacarpophalangeal joints are extended while the interphalangeal joints are flexed. The thumb again is opposed and slightly adducted. Active abduction and adduction movements of the finger are absent. The wrists are flexed - in one of them very acutely. Movements of the wrist joints are very markedly reduced.

Other Parts of the Upper Limb

The elbow usually shows some degree of flexion and active extension movement at this joint is almost invariably more limited than flexion movement. Contracture deformity at the elbow joint is of the flexion variety; but even in patients with fairly severe contracture of the elbow joint, active flexion is still possible to a greater or lesser extent. The shoulder joint does not show any definite deformity, although rigidity of adductors and internal rotators of the joint can be shown to be more marked than in the other muscles of the upper limb.

Pathogenesis of the Various Forms of Deformities of the Hand

1. Type of patient - whether ambulant or not:-

Table /

Fig. 25a. Right hand - Type III deformity.
Left hand - Type II deformity.

Fig. 25b. Lateral view of the right hand in Fig. 25a.

Type	No. of hands	% of total No. of hands	No. of Patients	% of total No. of patients
I	68	51.1%	44	65.6%
II	35	26.3%	20	29.8%
III	3	2.3%	2	2.9%
Normal	27	20.3%	18	26.8%

TABLE 10. Incidence of various types of deformities of the hand. (N.B. One patient had one arm amputated hence the odd number in the total number of hands).

Type of patient	No. of patients	No. of hands in each group			
		Type I deformity	Type II deformity	Type III deformity	normal
Ambulant	33	40	2	0	23
Non-Ambulant but able to sit in chair	21	22	16	2	2
Non-Ambulant and completely bedfast	13	6	17	1	2

TABLE 11. Incidence of the three types of deformities of the hand in ambulant and non-ambulant patients.

Type of patient	Males	Females	Total
Ambulant	19	14	33
Non-Ambulant (Chair)	6	15	21
Non-Ambulant (Completely bedfast)	7	6	13

TABLE 12. Sex distribution of ambulant and non-ambulant patients.

Table 11 shows the incidence of these three types of deformities of the hand in ambulant and non-ambulant patients. Out of the 33 ambulant patients only one (a woman) has Type II deformity and in this woman the deformity is of a very mild degree. The rest of the 33 patients in this group have either normal hands or the Type I deformity. There are 27 normal hands in the 67 patients, and 23 of them are from ambulant patients and 4 from non-ambulant patients.

Types II and III deformities are confined almost entirely to patients who are unable to walk, and especially in those that are completely bedfast. One may therefore conclude that Type II deformity is due to immobility and probably produced in the same way as flexion deformities and contractures, which are commonly seen in bedfast patients suffering from chronic illness or in the elderly who have been bedfast for some considerable period of time.

In keeping with what has been said of the association between Type II deformity and immobility, gross contractures are almost the rule in Type II deformity whilst contractures are rare in Type I deformity and when present, are of the mild variety. Contractures were present in 44 upper limbs out of which only 6 were found in the patients who were able to walk, and in these the contractures were mild.

2. <u>The degree of rigidity</u>:

The deformities also seem to be related to the degree of Parkinsonian rigidity. Thus 23 of the 27 normal hands in this series were found in ambulant patients and in most of these patients the rigidity /

rigidity was of a mild degree. It is also significant that in patients who have a normal hand on one side and a Type I deformity in the other, that the deformed side is the more rigid side. Furthermore, when a fully established Type I deformity and an early stage of Type I deformity occur in the same patient, the fully established deformity is on the more rigid side. In the non-ambulant patients (except one) it was also found that when Type I and Type II deformities exist in the same patient, that the Type II deformity is on the more rigid side. Cooper and Bravo (1958) have reported that deformities in Parkinsonism disappeared with the relief of rigidity following chemopallidectomy. In the course of the present investigation it has been found that when hyoscine is given subcutaneously, muscular rigidity is sufficiently reduced to cause considerable alleviation of "contracture deformity" and a similar but weaker effect is seen even after the oral administration of drugs such as orphenadrine (Figs. 26 a and b).

Contracture deformity is usually regarded as a permanent condition resulting from shortening of muscles and tendons (the consequent lengthening of antagonists is understood). However it should not be too readily assumed that the deformity is entirely attributable to these purely mechanical conditions. Sometimes reflex muscle contraction plays an important part in increasing a minor degree of permanent deformity. When reflex (postural) contraction of muscles is a factor, the differenciation is often possible. For example, therapy /

Fig. 26a. Gross contractures of the upper limbs. Patient was receiving Atropine 10 mg. thrice daily (orally).

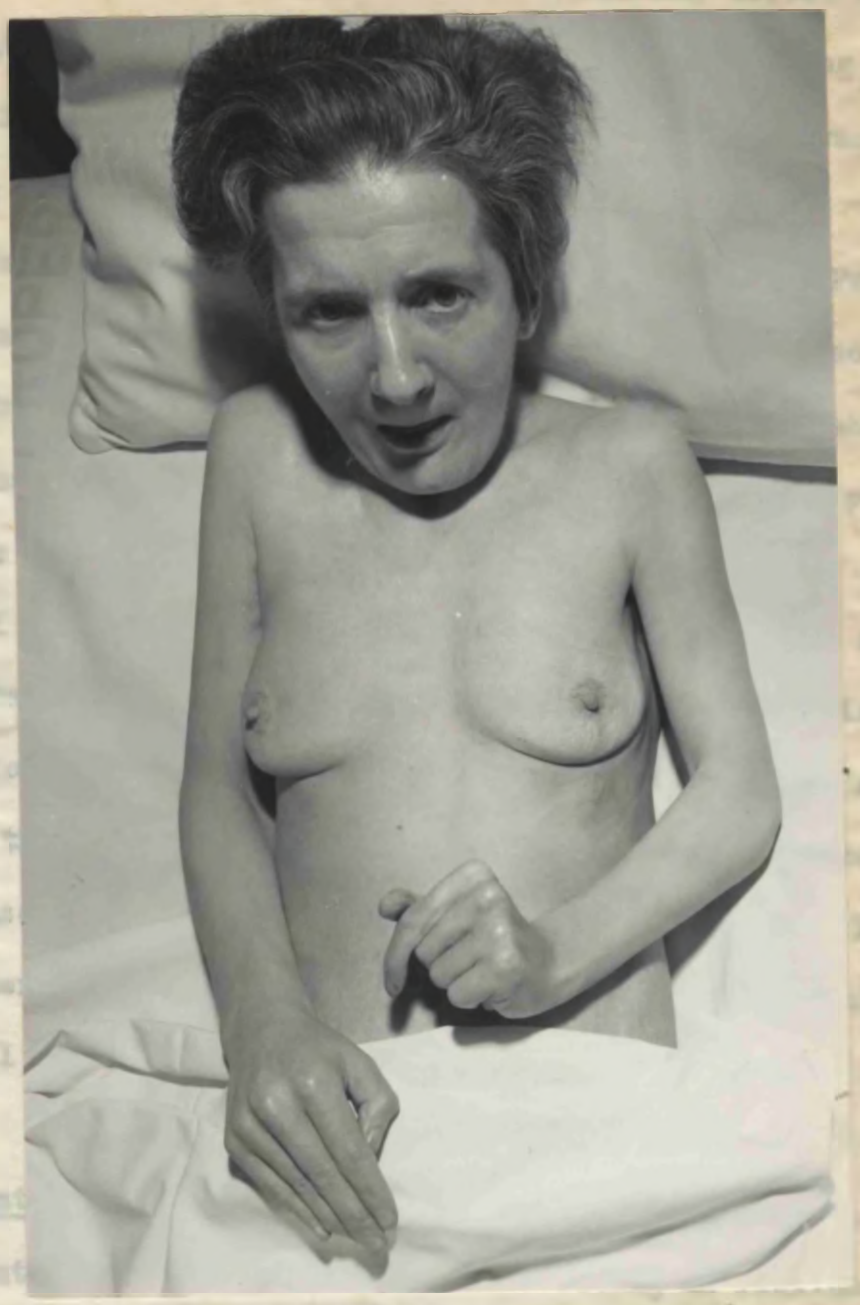


Fig. 26b. The same woman in Fig. 26a. Now receiving orphenadrine 100 mg. t.i.d.

Note considerable reduction in the degree of contractures at the elbow joints.

therapy which is known to reduce muscle tonus may effect considerable improvement in the condition of the joint notwithstanding that the deformity had been supposed to be due exclusively to permanent shortening (contracture) of the soft tissues.

One may therefore conclude that the deformities in Parkinsonism are certainly related to the degree of rigidity. It also seems that Type I deformity is the characteristic deformity of the hands in Parkinsonism occurring in 51% of the hands in 66% of the patients in this series (Table 10).

Type I deformity is similar to the main d'accoucheur deformity seen in tetany and sometimes in severe rheumatoid arthritis. This type of deformity is produced by the over-activity of the small muscles of the hand - the interossei, lumbricalis and adductor pollicis muscles which are supplied by the ulnar nerve. It is not clear whether the deformity in Parkinsonism is due to primary spasm in the small muscle of the hand or to over-excitability of the ulnar nerve.

3. Involuntary Spasms:

Involuntary spasms of the muscles resulting in flexion of the wrist and fingers were complained of by some of the patients with Type II deformity before contracture had set in. It was not possible to assess the importance of this phenomenon in relation to the pathogenesis of Type II deformity as these events had occurred several years earlier. Sciarra and Sprofkin (1953) reported on 474 patients with brain /

brain tumours, 10 of whom showed evidence of extrapyramidal involvement. One of the 10 patients developed advanced Type II deformity within one month following involuntary spasm of the muscles of the fingers. One of the patients (J.McM.) in my own series had normal hands when this survey was made, but subsequently developed involuntary flexor spasm of the left wrist and hand; within two weeks he developed permanent Type II deformity, although the spasms ceased after one week. The use of cock-up splint was not effective in preventing the deformity. In fact the patient found it rather irksome and sometimes painful, and so it had to be removed.

In experimental animals subjected to destructive lesions of the midbrain (especially when the lesions involve the medial longitudinal fasciculus and the red nucleus), involuntary spasms of groups of muscles and assumption of bizzare postures have been observed (Carpenter, Whittier and Mettler, 1950; Carea and Mettler, 1955). These findings suggest that in the post-encephalitic patient the spasms are likely to be due to the consequences of the midbrain disease rather than the result of independent changes in the cortico-spinal pathway.

4. Relative Strengths of Antagonistic Muscles:

The neutral position of a joint is due to the balanced action between the agonists and antagonists. As mentioned in Chapter I (page 47), the topographical distribution of rigidity in the voluntary muscles can be limited to one group of muscles. The rigidity and weakness /

weakness in one group of muscles will tend to create an imbalance in the mechanical pull on the joint, resulting in a new position depending on which group of muscles is stronger.

5. Type IIa deformity:

This is a variant of Type II deformity and it seems probable that it is produced by purely mechanical means. The terminal phalanges of the flexed finger come to be pressed against the thenar eminence and if the force is sufficiently great hyperextension of the distal interphalangeal joints will result, giving rise to what is called here a "Type IIa" deformity.

6. Type III deformity:

As already stated this deformity resembles the "claw hand" deformity of ulnar nerve palsy. Electrical studies using faradic stimulation were carried out in the two patients with this type of deformity to assess the state of the ulnar nerve: the nerve appeared to be normal. The radial nerves were also intact in these two patients - and also in three patients who had this test carried out during investigation of flexion deformity of the wrist joint. Details of the results of the electrical studies in these two patients are given below. Results of electrical studies of the muscles which move the ankle joint and the foot are also recorded.

K. Has. Woman aged 46 years. Admitted 1950.

No history of encephalitis lethargica. "Dizzy turns" for 2½ years. /

years. Slight haematemesis one week before admission.

On examination (1950). Thin woman. Rigidity left upper and lower limbs. Involuntary tremor all limbs (left greater than right). Poor muscle power all limbs.

Re-assessment after 10 years (1960). Bedfast. Very marked rigidity (Grade 3) all limbs but especially on the left side. Tremor very slight. Deep reflexes could not be elicited. Minimal general wasting of all limbs.

Deformities:

Hands. Type III with gross flexion contractures of both wrists and both elbows.

Lower Limbs. Right knee - flexion contracture.
Left knee - contracture in extension.
Foot and ankle - plantar flexion with slight eversion right side.

Results of Faradic Stimulation at the Motor Points of the Muscles.

Left Hand and Wrist (more deformed than the right).

1. Common Extensor Muscles: Excitable but stimuli (weak to moderate) produced no movement of the wrist. On increasing the strength of stimulation, flexion of the wrist resulted instead of extension. No movement of the fingers was produced.

2. Dorsal Interossei: Responded to Faradism, but a form of mass action resulted; stimulation of the third or fourth dorsal interosseus muscle /

muscle caused all the interossei muscles to contract.

Right Hand and Wrist

1. Common Extensor Muscles: Excitable, but extension occurred mainly at the metacarpo-phalangeal joints. No flexion of the wrist resulted on increasing the strength of stimulation (c.f. left hand, above).

2. Dorsal Interossei: Excitable, and produced the usual abduction movement of the fingers. There was no spreading of the effect from one muscle to its neighbours as on the left hand.

Comment

The response of the extensor muscles and the dorsal interossei to Faradism rules out radial and ulnar nerve palsy. It is difficult to explain the production of flexion of the wrist while the extensors were being stimulated. It was presumably due to a spread of current to the flexors of the wrist. The result is however in keeping with the view that when flexors and extensors are stimulated simultaneously it is the action of the flexors that predominates. In this patient it is reasonable to assume that the flexion deformity of the wrist is due to the fact that the extensors of the wrists are very much weaker than the flexors. The cause of the spread of current from the extensors to the flexors is not known but wasting of the muscles may be a factor.

Lower Limbs:

Left Leg /

Lower Limbs:

Left Leg

Tibialis Anterior - Excitable, but stimulation caused weak extension (dorsiflexion) of the ankle.

Extensor Digitorum Longus - Excitable with normal action (extension of the toes).

Gastrocnemius Muscle - Normal action.

Soleus Muscle - Normal action of plantar flexion.

Right Leg

Tibialis Anterior Muscle - Excitable, but stimulation produced no extension of the ankle or inversion of the foot. There was a tendency to flexion of the toes and even flexion of the knee. By stimulation applied along the anterior surface of the leg, flexion of the toes resulted from small currents which produced no visible or palpable contraction of the tibialis anterior.

The Gastrocnemius and Soleus Muscles - Excitable, with the normal action of plantar flexion.

Comment

In order to assess the significance of results obtained from these tests made on patients, similar procedures were carried out on the examiner and on the physiotherapist, using the same strength of current and applying the electrodes in the same places. Two important control observations were thus made: (1) contraction of the underlying /

underlying muscle was elicited as expected; (2) there was no spreading of the stimulus to other muscle groups. It is clear therefore that in the case of the post-encephalitic (K.Has.) there was an abnormality in the behaviour of the tibialis anterior muscle when under active stimulation.

C. McK. Woman aged 58 years. Admitted 1930.

Para 4 (1922, 1924, 1926 and 1927). The last two babies died in the neonatal periods.

1924 "Influenza" lasting two weeks. Insomnia and diplopia. Diplopia continued until 1960.

1926 Onset of oculogyric crises.

On examination 1960. Bedfast. Marked rigidity all limbs (left greater right) : lower limbs Grade 3 and upper limbs Grade 2 to 2+. Wasting both sides, worse on the left. Deep reflexes could not be elicited.

Deformities. Flexion contractures both wrists and elbows.

Hands. Right - Type III. Left - Type II

Knees. Flexion contractures.

Feet and Ankles. Talipes equinovarus deformity both sides (worse on the right).

Results of Faradic Stimulation at the Motor Points of the Muscles.

Hands and Wrists /

Hands and Wrists

Intact radial and ulnar nerves. There was no spread of impulses when the dorsal interossei were stimulated.

Extension of the wrist was weak but that of the metacarpo-phalangeal joint was more powerful. There was no spread to the flexors of the wrist when the extensors were stimulated.

Legs

Right Foot

Tibialis Anterior Muscle - Excitable, and stimulation resulted in well marked inversion of the foot. However plantar flexion of the ankle resulted instead of dorsiflexion. The calf muscles were felt to contract and the contraction was more powerful than that of the tibialis anterior which was being stimulated. This was interpreted as an "escape" of the stimulus so that it affected the flexors also; and when these contracted they dominated the picture.

Extensor Hallucis Longus and Extensor Digitorum Muscles - Responded to Faradism and showed normal reaction of extension of the toes. There was no spread to the calf muscles.

Gastrocnemius Muscle - Normal action.

Soleus Muscle - Normal action.

Left Leg. (More wasted than the right, especially at the calf).

Tibialis Anterior Muscle - Normal function, contraction quite strong with extension of the ankle and inversion of the foot. There was no spread to the calf muscles.

Extensor /

Extensor Digitorum and Extensor Hallucis Longus Muscles - Normal action.

Gastrocnemius and Soleus Muscles - Normal function.

Comment

1. The left leg was more wasted than the right but deformity was greater in the right leg.

The strength of the tibialis anterior was greater on the left side. This probably explains why the plantar flexion deformity was greater on the right side.

2. If it is true that the spread of stimuli is due to wasting of muscles, then it is difficult to explain why the spread of current from tibialis anterior to the calf muscles was confined to the right leg which was less wasted than the left. It would appear, therefore, that there are other contributing factors.

Deformities of the Lower Limbs:

Ankle and Foot. Plantar flexion was the most common deformity: it was present in 85 out of 128 feet (66.2%). The disability was often aggravated by inversion: this was seen in 40 of the 85 feet with plantar flexion deformity (47%). The talipes equinovarus deformity (plantar flexion + inversion of the foot) may be severe enough to give one the impression that there is sub-luxation of the talus (Fig. 27a). X-ray in the more gross cases, however, revealed no subluxation (Fig. 27b). In one patient there was Pes Cavus in addition /

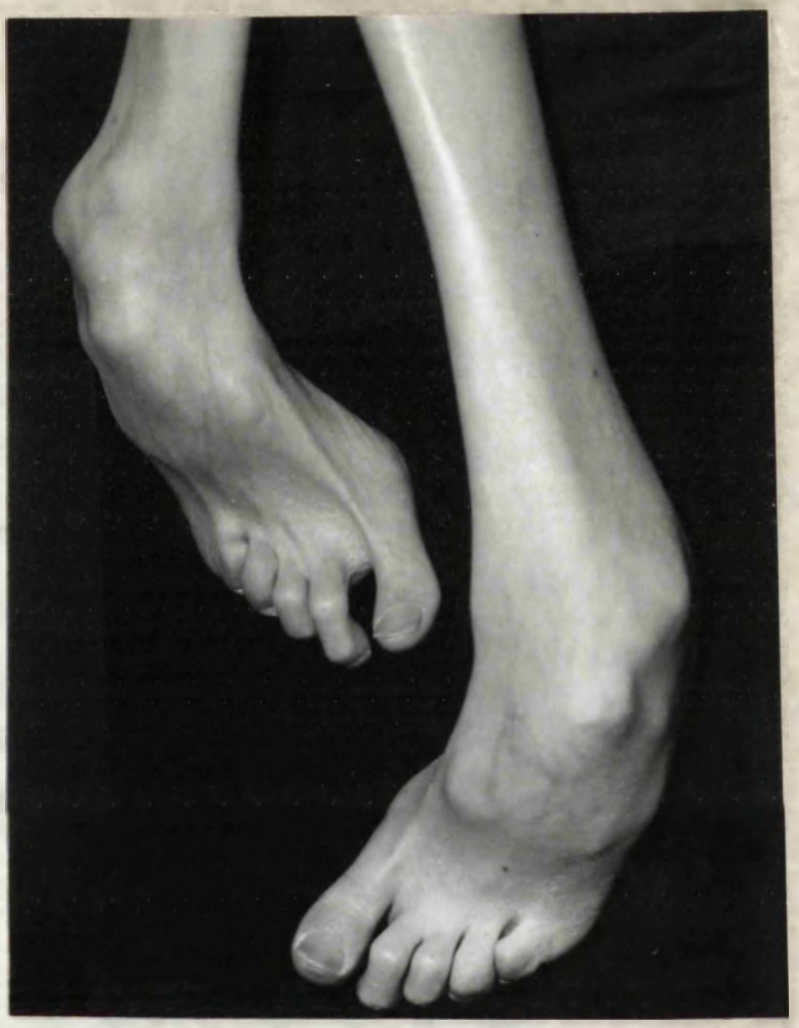


Fig. 27a. Typical talipes equino varus deformity in post-encephalitic Parkinsonism.

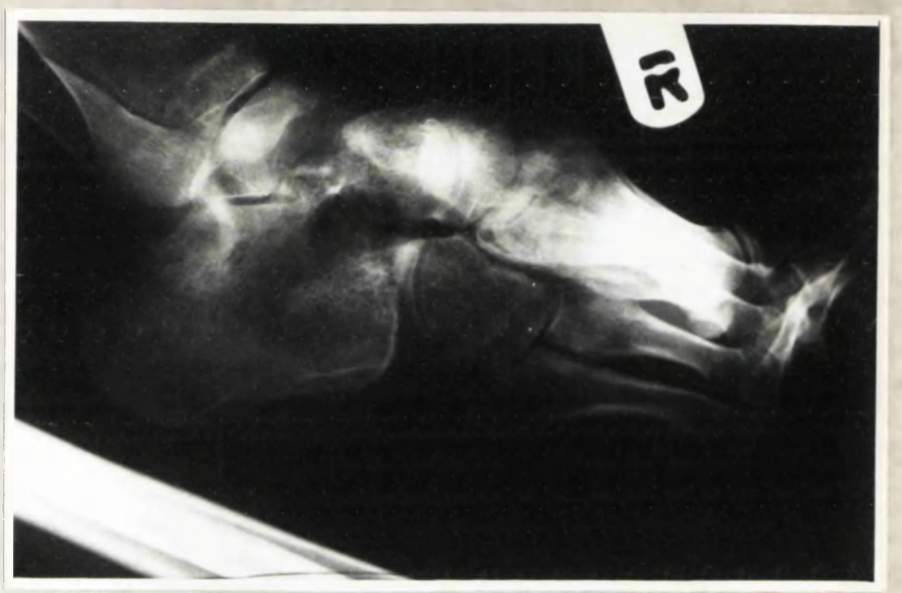


Fig. 27b. X-ray of the right foot and ankle. There is no coincidence of sub-luxation of talus or the tarsal bones.

addition to the talipes equino varus deformity (Fig. 28).

Knees. In the erect posture the Parkinsonian patient tends to assume a flexed attitude at the knee joint. The incidence of contractures of the knee joint is of some interest. Of the 128 lower limbs (64 patients) studied, contracture at the knee joint was present in 49 (38%). In one only was the knee in extension; the rest were flexion contractures. Six of the contractures occurred in ambulant patients and the rest were seen in those unable to walk - and especially in patients who were completely bedfast. It appears that women are more prone than men to develop contracture. Of the 43 contractures of the knee seen in the 31 non-ambulant patients 13 men and 18 women), 15 were in men and 28 in women.

Hip Joints. No definite deformity was detected but rigidity of adductor muscles of the hip joint was usually more marked than in any other group of muscles.

Pathogenesis of the deformities of the Lower Limbs.

The factors are similar to some of those mentioned in respect of deformities of the hand and will therefore be discussed briefly:

1. The type of patient (whether ambulant or not). The more severe deformities are seen only in patients unable to walk. Deformities are also more frequent in the bedridden than in ambulant patients. 35 out of 66 feet (53%) in walking patients were normal while only 7 out of 62 feet (11%) in non-ambulant patients were normal.

2. /

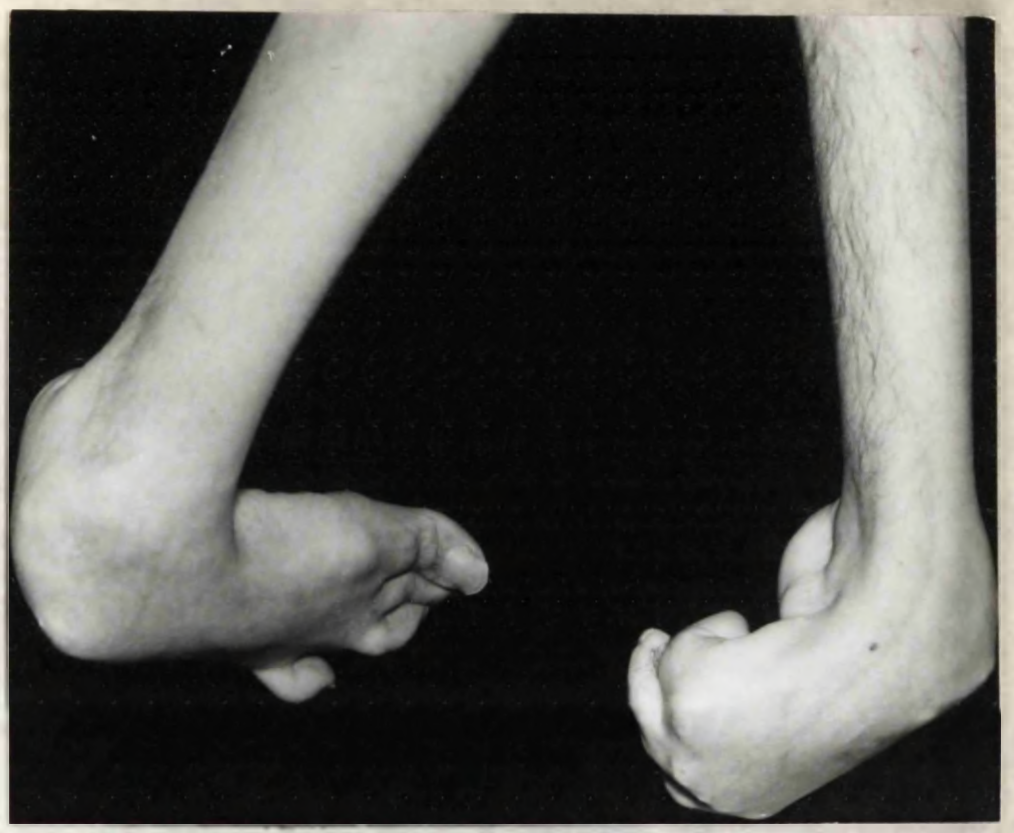


Fig. 28. Gross deformities of both feet. In addition to the talipes equino varus deformity on both sides, pes cavus is also present on the left side.

2. The degree of rigidity. The more rigid side is invariably the more deformed side. If one side is normal and the other deformed, the deformed side is the more rigid side. The circumstances are apt to create a vicious circle: spasticity not only predisposes to deformity, it also interferes with walking; and eventually the disability may result in the patient's becoming bedridden - a state which increases the likelihood that deformities will develop.

3. Involuntary spasm. The role of involuntary spasm in the production of talipes equino deformity is not known. It was however observed that in one patient involuntary spasms of the calf muscles were frequently present and this led to plantar flexion of the ankle joint.

4. Relative strengths of opposing or antagonistic muscles acting on a joint. The neutral position of the ankle joint depends on the balance of the power of dorsiflexors of ankle joint (chiefly the tibialis anterior muscle) and the plantar flexors especially the gastrocnemius and the soleus muscles. From studies involving the use of electrical stimulation of muscle groups, it appears that plantar flexion can result from relative weakness of the tibialis anterior muscle and consequent predominance of the calf muscles.

Deformities of the Spine

Deformities affecting some part of the spine are very common in Parkinsonism. The present observations refer only to scoliotic abnormalities /

abnormalities as the common-place kyphotic deformity has been fully described in the literature.

Deformities of the neck

and the cervical spine:

The degree of lateral flexion of the neck was assessed in all the patients but it was thought that only in the ambulant patients would this study be informative, as the state of bedfastness affects the position of the neck in ways that are controlled with difficulty if at all.

18 of the 33 ambulant patients had deformities of the neck with varying degree of lateral flexion of the neck. In 15 of the 18 patients (83.6%) the neck was laterally flexed to the less rigid side. The remaining 3 patients (16.4%) had lateral flexion of the neck to the side with greater rigidity. Figs. 29a and 30 show the examples of the deformities of the neck; and Fig. 29b is a radiogram of the cervical spine and it shows the scoliotic deformity of the cervical spine in association with the lateral flexion deformity of the neck.

Scoliosis of the thoracolumbar spine:

This study was again confined to ambulant patients in order to avoid the effects of bedfastness. There were five patients (3 men and 2 women) with marked scoliosis of the thoracolumbar spine. In the 3 male patients the scoliosis was concave to the less rigid side. In one of the female patients the scoliosis was, however, concave to the more rigid side. In the other female patient, the scoliosis was maximal /

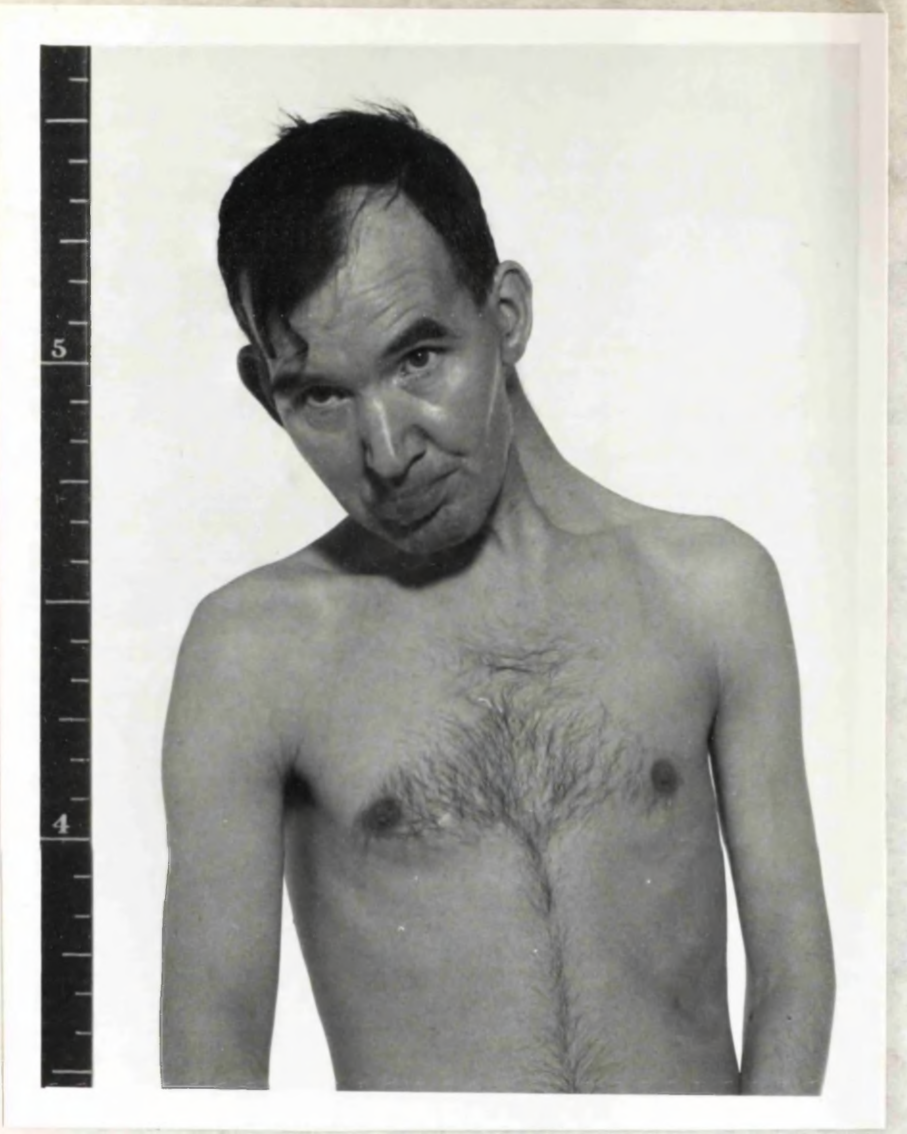


Fig. 29a.

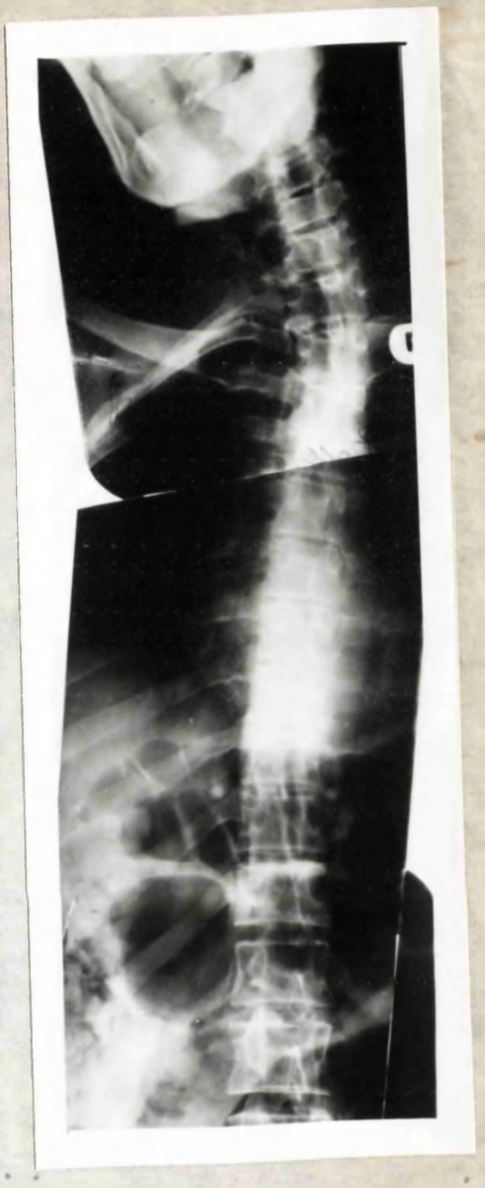


Fig. 29b.

Fig. 29a. Lateral flexion deformity of the neck. Left side much more rigid than the right.

Fig. 29b. Radiograph of the vertebral column showing a scoliotic deformity of the cervical spine convex to the more rigid side.

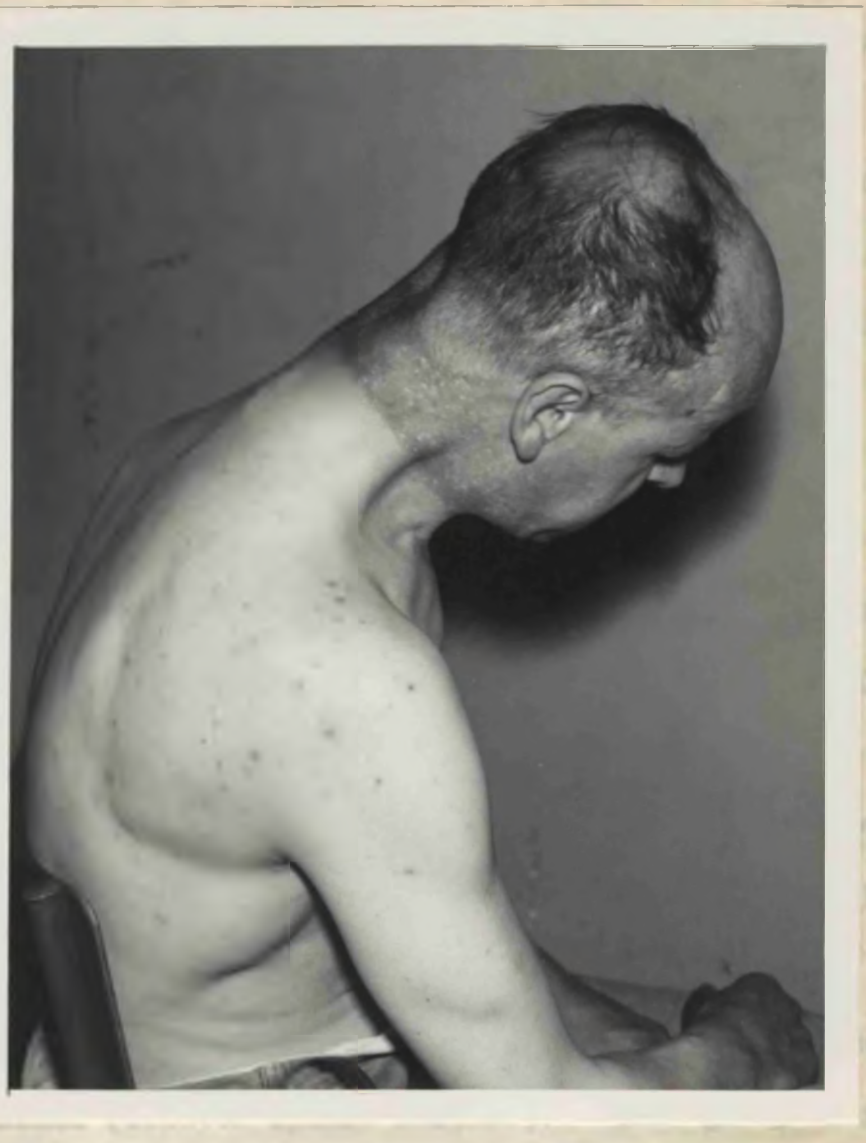


Fig. 30. Another patient with gross lateral flexion deformity of the neck. (Left side more rigid than the right side).

maximal in the lumbar region (Fig. 31b). In this patient the upper limb was more rigid on the right side while the lower limbs were more rigid on the opposite (left) side. The lumbar scoliosis was similar to that seen in the male patients, concave to the less rigid side of the lower limbs. It would appear therefore that in cases of scoliosis in Parkinsonism, the scoliosis is usually concave to the less rigid side. Figs. 32 a and b are radiographs of the spines of patients shown in Figs. 31 a and c.

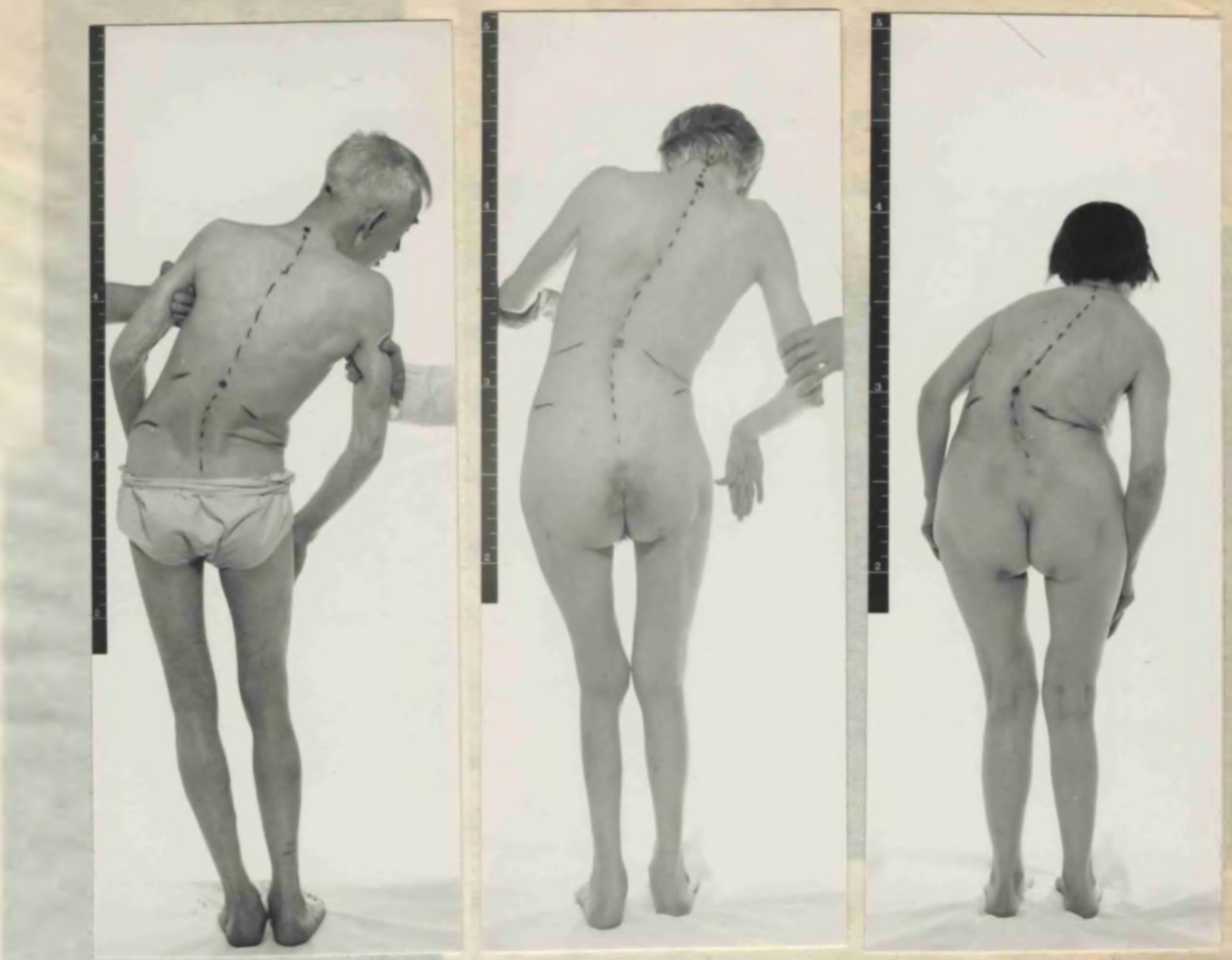
Mode of production of scoliosis

The central or neutral position of the spine is due to a balanced action of the muscles which act on both sides of the spine, namely the pre- and post-vertebral muscles, the sternomastoids, the scaleni and the anterior abdominal muscles. In order to understand the mode of production of scoliosis it is necessary to understand how movements of the vertebral column are produced. A good account of this has been given by Last (1954).

Extension of the spine is produced by the action of the post-vertebral muscles (erector spinae muscles). This group of muscles is more bulky and more powerful than the pre-vertebral group. Flexion of the spine is produced partly by the action of the prevertebral muscles but the chief flexors of the spine are the sternomastoid and the rectus abdominis muscles.

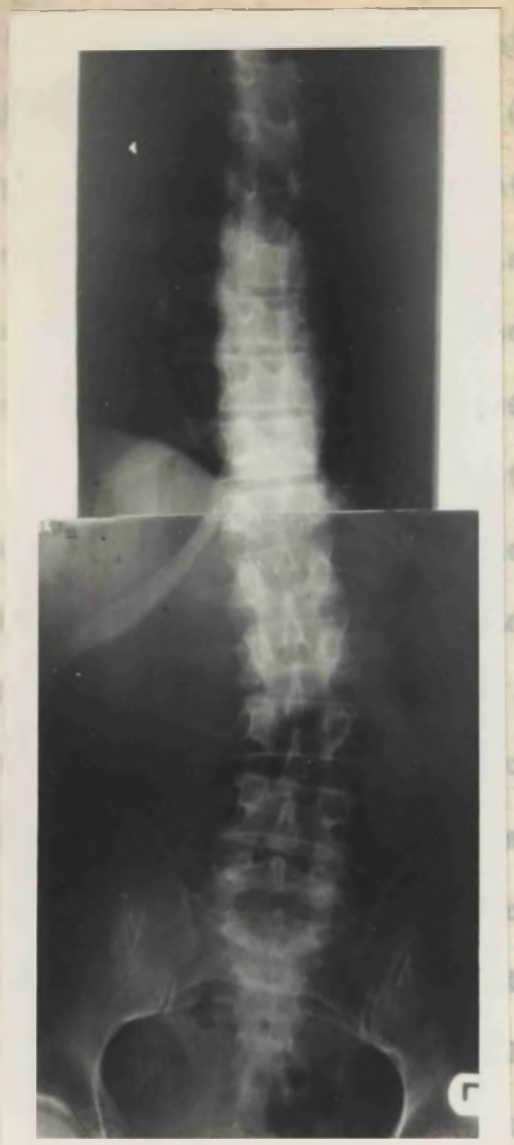
Lateral flexion is due to the action of the erector spinae, oblique muscles of the anterior abdominal muscles and the sterno-

mastoid /

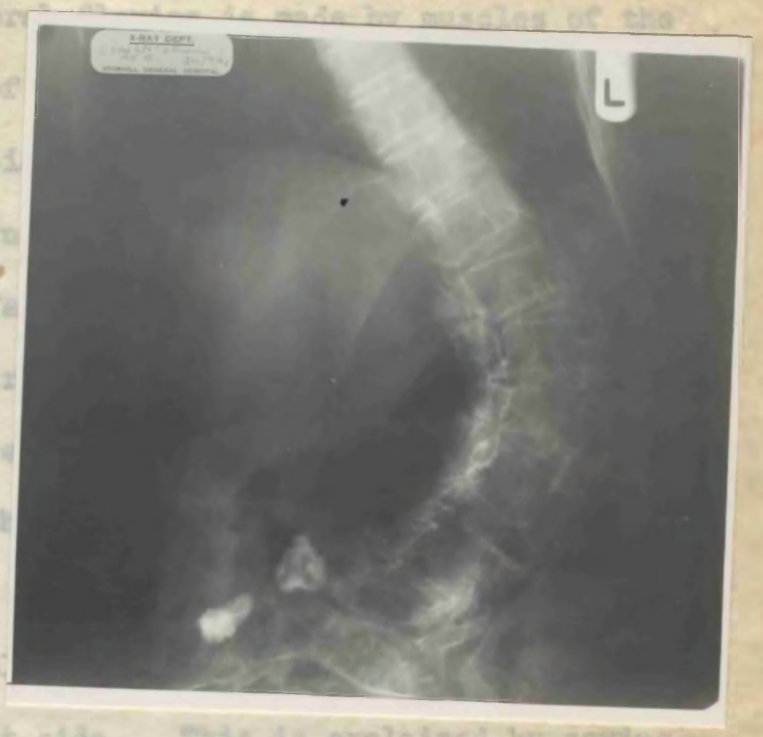


(a) (b) (c)

Fig. 31. Three patients with gross scoliotic deformity of the thoraco-lumbar spine.



(a)



(b)

Fig. 32.

(a) Radiograph of the spine of the patient shown in Fig. 31a. Scoliosis is confined mainly to the lumbar vertebrae.

(b) Radiograph of the patient shown in Fig. 31c. Gross scoliotic deformity of the thoraco-lumbar spine.

sternomastoid and the scaleni - acting of course on one side only. Lockhart, Hamilton and Fyfe (1959) in discussing the action of the post-vertebral muscles in lateral flexion of the spine, state that in the presence of resistance lateral flexion is made by muscles of the same side, and in the absence of resistance by relaxation under tension of the muscle of the opposite side.

The influence of the sternomastoids on the position of the neck and the spine is shown by the fact that "wry neck" or torticollis can be produced by spasm (contracture) of the sternomastoid on one side. Contraction or shortening of the sternomastoid on one side causes the ear of the same side to approach the tip of the shoulder with the chin rotating to the opposite side.

After unilateral thoracoplasty operation on the scoliosis that results is concave to the intact side. This is explained by saying that the operated side is relatively unsupported and therefore weaker; thus the normal side exerts unopposed muscle tensions which bend the spine (like a bow with a tight string) and resulting in a scoliosis concave to the intact side.

This situation is reproduced in all essentials in patients suffering from scoliosis which is the result of Parkinsonism. It must be noted however that the muscles on the rigid side of the body are relatively weak. The muscles on the less rigid side of the body are relatively strong and it is these which over-act; their over-activity flexes the spine so that the concavity of the scoliosis is towards the less rigid side of the body.

MANAGEMENT OF DEFORMITIES IN PARKINSONISM AND THE CARE OF THE SKIN

Excessive salivation shown by dribbling of saliva from the mouth appears to have three contributory causes:-

1. The characteristic forward and/or lateral flexion of the neck:

This prevents the normal drainage of saliva into the pharynx. The effect of posture is often apparent in patients with scoliosis of the cervical spine: the ordinary night-gown worn by these patients hangs crookedly from the asymmetrical shoulders. The attitude of the head and face is that associated with chronic wry neck: the plane of the mouth is slanted and saliva dribbles from the angle which is lower. If the patient has been eating coloured foodstuff (for example, chocolate or sweets) the saliva stains the clothing on one side (the lapel and adjacent areas) whereas the other side remains clean.

2. Dysfunction of the swallowing reflex:

Normally accummulations of saliva are disposed of reflexly and without any conscious effort. It is conceivable that if the muscles of deglutition are rigid from Parkinsonism the operation of the motor side of the reflex arc will be hindered and reflex swallowing of saliva will occur less frequently: thus there will be excessive accumulation of saliva in the mouth and dribbling will tend to occur.

3. Some actual increase in the secretion of saliva (sialorrhoea):

It /

It seems probable that in some patients there is an absolute increase in the secretory activity of the salivary glands. There are patients who, when placed on placebo therapy, report that they have to make a special effort to swallow saliva as the mouth is frequently full of secretion. Examination of the mouth then reveals a very moist tongue and often a pool of saliva on the floor of the mouth.

Excessive salivation accompanied by dribbling is a humiliating disability - especially to the intelligent patient. In addition, the state of the patient and his clothing occasioned by the dribbling of saliva is unpleasant for those around him. It is thought that of three factors responsible for the dribbling of saliva, the effect of posture is probably the most important. Consideration was therefore given to measures calculated to control the dribbling of saliva simply by attending to the postural abnormality. One advantage of successful orthopaedic management would be the elimination of the use of the atropine group of drugs to supplement the newer synthetic preparations when the latter drugs do not adequately control the excess salivation.

Four patients with excessive salivation and marked dribbling of saliva were selected for this study. Two of them have gross scoliosis of the spine; the other two (one man and one woman) have mainly a forward flexion of the cervical spine. The problem was tackled with greater optimism in the patients with only forward flexion of the neck and the splint that is described below was constructed for the reduction of forward flexion deformity only. The splint was designed in close /

close collaboration with the splint makers, Messrs. G.B. Ritchie and Co., Ltd., Surgical Instrument Makers, Glasgow, and Mr. J.M. Main, F.R.C.S.

Essential requirements of the splint.

Three requirements were considered essential for such a splint which was to be worn during the day and removed during the night:-

1. Light in weight and yet be strong enough to support the head.
2. Capable of fine adjustment.
3. Easy to fit on and to wear.

Description of splint (Fig. 33).

The splint consists essentially of two "shelves", one to support the lower jaw and the other to support the occiput. Each shelf consists of a metallic basis covered with sorbo-rubber. Each shelf is supported by two vertical adjustable metallic props resting below on a chest plate which is padded with felt. The splint is in two separate parts - a front and back piece and these are connected together by adjustable leather straps.

As a preliminary to making the splint, a plaster of Paris (P.O.P) collar splint was applied fairly closely while the deformity was slightly over-corrected. The P.O.P. collar splint was split on either side into two pieces soon after it had set. The splint makers constructed the metalic splint described above using the measurements obtained from the P.O.P. cast.

RESULT /

Fig. 33. Adjustable splint for correcting forward flexion deformity of the neck.

1. Adjustable strap.
2. Anterior or chin shelf.
3. Adjustable supports.
4. Chest plate.
5. Adjustable straps.
6. Posterior or occipital shelf.

RESULT

When the splint was strapped in place with the head and neck in a neutral position it was noticeable that dribbling of saliva abated although the mouth and tongue were still excessively moist. In other words dribbling of saliva was relieved. It was not possible to comment on the rate of production of saliva but there was no reason to suppose that the volume of secretion had diminished. Unfortunately, however, after a few hours the anterior shelf usually slipped backwards so that the anterior aspect of the mandible was no longer resting on the shelf. The slipping of the anterior shelf was explained thus: when the splint was fixed in position with the head and neck in neutral position the upper surface of the shelf sloped somewhat backwards instead of forward. In spite of some adjustments by the makers, this difficulty was not overcome; the shelf continued to slip out and hence frequent adjustment of the splint was necessary. The circumstances caused some distress to the patients - few of whom are tolerant of adverse conditions calling for a measure of endurance and perseverance. It was therefore necessary to abandon the experiment. Notwithstanding that the patients were unwilling to persevere with the splints for adequate periods of time and that the splints were not ideal in their design, this limited study showed clearly that even where there is an excessive secretion of saliva, dribbling from the mouth results from a reversal of the normal direction of flow and that this is the consequence of faulty posture.

With regard to the other two patients with more extensive and severe /

severe deformities of the vertebral column, for reasons that will be clear later, it was not possible to devise suitable splints. The splint was extensive, being in the shape of a collar splint above, and of a hip spica below. In order to make the P.O.P. cast from which the splint was made, the deformity had to be corrected under general anaesthesia. The splint was to be worn only during the day; and it was found that it could be properly applied only following the daily administration of muscle relaxants. The splint was designed by Mr. J. Main, surgeon at Stobhill General Hospital. These circumstances made it necessary to abandon the use of the splint.

A simple procedure in the management of these patients is to ensure that when sitting, the type of chair used is one which ensures drainage of saliva backwards to the fauces. It has been found that a high-backed chair tilted backwards by lengthening the front legs of the chair often contributes considerably to the alleviation of this symptom for part of the day.

Medical Management of Deformities of the Hand:

Deformities of the hand also received some attention. In Type II deformity where the fingers are tightly flexed, it was found that the skin of the palm of the hand became macerated by sweat and this predisposed to local infection, ulceration and the formation of offensive discharge. The routine treatment by the nursing staff had consisted of the use of liberal amounts of dusting powder to keep the area dry. In a few cases, ulceration of the finger or the palm may occur /

occur in spite of these preventive methods. One patient developed chronic ulceration of the palmar surface of the middle and ring fingers of the right hand. The ulcer did not improve on various kinds of conventional treatment and amputation of some of the fingers was considered. Indeed the patient herself volunteered the suggestion that amputation should be performed. After discussion, however, a method was devised for thoroughly ventilating the skin of the palm. Warm air was blown into the enclosed space by means of an electric hair-dryer and vaseline gauze was applied to the ulcer craters. The tissues soon became more wholesome, and in the course of a few weeks the ulcers had healed.

The methods described were based on physiological principles which have been accepted for a long time in clinical practice. The skin is designed to desquamate and provision is made for continuous renewal of the cells lost from the body surface. Such a mechanism is clearly indispensable for highly mobile organisms whose body movements result in surface friction; and the complementary situation is that in health such conditions themselves are potent in stimulating regeneration of surface epithelium. There are circumstances, however, in which this activity of the skin can become a source of danger. If a limb is immobilised - and especially if this is the result of muscle weakness and contracture deformity of the limb - complete desquamation is impeded, the stratum corneum is macerated by sweat, moist epithelial debris accumulates and provides an excellent culture medium for bacterial growth and the proliferation of yeasts. Thus local infection /

infection spreads into the cutis vera and superficial tissues, resulting in cellulitis and ulceration.

In order to separate the fingers from one another and also to prevent prolonged apposition of the fingers and palm, lamb's-wool was used as insulating material. There are several advantages in using this wool: it is light in weight and very soft to the touch. Most important of all the fibres have retained enough lanolin to resist the tendency of moisture to produce the sodden state: water vapour from the skin percolates in the spaces created by the filaments and can thus escape from the body surface. By comparison, cotton used as "cotton-wool", is very unsatisfactory: matting of the fibres soon occurs when the material is packed into spaces surrounding the sweating skin, and the sodden pack produces effects which are just the opposite of those which are desired. In practice amongst post-encephalitic patients, these advantages in the use of lamb's-wool were immediately obvious. In bedridden patients maceration of the skin of the legs is likely to occur if one limb is allowed to rest across the other for an hour or so; and this can hardly be avoided in the helpless post-encephalitic (unable as he is to turn in bed), and some have the additional handicap of flexion deformity with adductor spasm. In such circumstances large pads of lamb's-wool were placed between the opposing surfaces. It was found helpful to enclose these masses of wool in nylon hair nets. Allergic dermatoses are sometimes caused by wool, but no cases of this type have so fare occurred.

As /

As in all paralytic diseases complicated by contractures, mechanical devices of one kind or another are likely to be tried as aids to minimising the consequent disabilities. In such circumstances success or failure may depend in some measure on maintaining a healthy and intact skin. General hygiene must therefore receive scrupulous attention to combat the effects of excessive production of sweat and sebaceous secretion - characteristic of the post-encephalitic. A greasy scalp is a common source of trouble with its attendant seborrhoeic dermatitis of the face, the neck, and the anterior aspect of the chest. This condition is readily controlled by the "sulphur shampoo" regimen carried out every three or four weeks as an addition to routine hygiene. The use of Selenium Sulphide has been found to be an effective method of combatting seborrhoea of the scalp, but the older, conventional methods are probably equally satisfactory such as the use of Sulphur Compound Lotion (BNF) followed by a soap shampoo.

SUMMARY

The deformities of the hand in post-encephalitic Parkinsonism have been classified as Types I, II, and III. Type I (main d'accouchūer deformity) is the most common form.

Talipes equino varus deformity is the common deformity of the foot in Parkinsonism.

Scoliotic deformity of the spine, especially of the cervical spine, is common. The scoliosis is usually concave to the less rigid side.

The factors of importance in the pathogenesis of deformities include: skeletal muscular weakness, rigidity and involuntary muscle spasms. Muscle weakness is the most important factor. It is emphasised that deformity is not due to the action of the rigid muscles (as is commonly thought), but results from an uncounterbalanced action of the stronger and less rigid muscles. The opposing weaker and more rigid muscles are lengthened as a result.

It is suggested that the effect of posture is probably the most important factor responsible for dribbling of saliva.

The use of splints and lamb's-wool in the management of some types of deformities is discussed.

C H A P T E R V I.

ASSESSMENT OF DRUG THERAPY IN PARKINSONISM

INTRODUCTION

The disabilities associated with Parkinsonism are often serious and over a long period of years, they are usually progressive. There is no specific treatment for the disease as seen in its common forms. It is therefore particularly important to ensure that the most effective kinds of palliative treatment is provided for the individual patient. Such treatment include drug therapy. New pharmaceutical preparations are increasingly offered for clinical use by manufacturers. The evaluation of these substances presents exceptional difficulties. Clinical trials on the actual patients are indispensable, but it is by no means common to find adequate numbers of patients conveniently segregated in hospital and willing to submit to measurements which are necessarily exacting for all concerned. The burden imposed on volunteers is obvious when the conventional designs of clinical trials are studied. Experience over a period of three years, while looking after over 60 post-encephalitics, abundantly confirms the need to adopt the classic methods of the double-blind technique. Casual observations are of limited value and among long term patients of this kind there are many pitfalls awaiting the clinical /

clinical pharmacologist who relies on a limited selection of data.

One example of the difficulties confronting the clinical pharmacologist is concerned with patients' attitudes and motives. Their disabilities inevitably create feelings of dependence and these are naturally manifested in their relation to the nursing staff and the doctor. A patient may therefore be reluctant to offer any comment about treatment if he thinks his remarks might be construed as criticism of the doctor or dissatisfaction in general. The tendency of these patients to make statements calculated "to please the doctor" can easily vitiate the conclusions reached in a clinical trial unless stringent safeguards are adopted. Thus the use of placebos is indispensable and at all times care must be taken to adhere to a standard method of investigation while eliciting information about subjective responses to therapy.

It is already established that certain synthetic compounds such as benzhexol and orphenadrine give substantial relief in Parkinsonism. Any new drug for use in the disease must stand comparison with the current official preparations.

In the following report this kind of investigation has been carried out to assess the therapeutic value of N-ethyl-nortropine benzhydryl ether hydromide (prepared by Messrs. Sandoz Products Ltd. and designated "UK. 738"). The effects of this drug have been compared with those of orphenadrine and suitable placebos have also been used. /

used. Orphenadrine (Disipal) was chosen because it has been rated as the most effective single drug in the treatment of Parkinsonism (Gillhespy, 1956).

The study was undertaken with two objectives in view:-

1. To assess the therapeutic value of UK. 738 and also that of orphenadrine.
2. To determine the value of objective measurements in this assessment. Hitherto, there has been considerable controversy as to the value of objective measurements (Gillhespy and Ratcliffe, 1956; Schwab and Leigh, 1949; Berkowitz and Alverman, 1952).

Although this was not the objective in this study, it was considered that this clinical trial might afford an opportunity to study the more florid manifestations of Parkinsonism.

Two types of studies were carried out. The first was a double-blind trial in which UK. 738, orphenadrine and their placebos were used. The second was an "acute" study designed to determine the length of time between the taking of a drug and the onset of therapeutic effects and to ascertain if there was a phase of peak activity in the pharmacological action.

METHOD AND MATERIAL

Double Blind Trial:

Twenty-four patients were studied. Some of them were ambulant and some were bed patients. Their ages ranged from 42 years to 62 years with an average age of 53 years (three-quarters of them were in the 49 to 58 year age group).

Selection of patients

As stated in earlier chapters, there was a total of 67 patients in the post-encephalitic wards. These patients were suffering from Parkinsonism of varying degrees of severity; some of them being very ill and severely disabled; a few were curled up in a state of generalised flexion deformity; others were unable to speak intelligibly and communicated by signs; a few were of low intelligence and had deteriorated further as a result of long-standing Parkinsonism. It was therefore essential to select the patients who were to take part in this clinical trial. Certain criteria were therefore adopted for the inclusion of a patient in the trial and these were as follows:-

1. The patient should not have gross deformities, especially of the hand. It was essential that the patient should be capable of using at least one hand so that the strength of grip could be measured.

2. /

2. It was desirable to study the effects of the drugs on oculogyric and sweating crises and it was therefore decided to include at least 10 patients suffering from these crises.
3. The patients should suffer from Parkinsonism of moderate severity although a few patients with rather severe disabilities were ultimately included.

The patients were studied in two groups of 12 (6 men and 6 women in each group). The number was kept small in order that the patients might be observed in greater detail. As "Disipal" and "UK. 738" tablets were of different colours, two placebos had to be used in order to eliminate the psychological effect known to be associated with the mere colour of a tablet.

Each drug (including the placebos) was given in a dosage of two tablets three times daily for three weeks. A master chart was prepared so that the drugs were given in a randomised fashion. This chart was given to the pharmacist, and he allocated at random various letters of the alphabet to each of the four types of tablet. Only the pharmacist had access to the key which identified the tablets. Every Saturday he sent to the wards individual packets of tablets for the patients. The label on each packet showed the patient's name, the date and the direction to take two tablets three times daily. No other information was given.

In /

In order to minimise the risks of precipitating withdrawal syndromes (when changing from an active drug to a placebo), a scheme was devised to effect overlapping of treatments at the week-end. Thus patients received on Saturday afternoon two tablets of the new set instead of the tablets in current use and on Sunday two tablets of the new set in the morning and evening, the set of tablets in current use being given only in the afternoon. From Monday to Friday the new set of tablets was given as usual (two tablets thrice daily) (Table 13). When, over a period of some days, a patient appeared to be lapsing into a state of serious disability while taking a particular type of tablet, the treatment was stopped and the pharmacist was asked to supply to the patient the next type of tablets on the chart. The tablets were given at definite times, namely 8.45 a.m., 1 p.m. and 6 p.m.

Day	Tablet		
Friday	A	A	A
Saturday	A	B	A
Sunday	B	A	B
Monday	B	B	B

TABLE 13

Scheme devised for overlapping treatment at the weekend.

A = Tablet in use in the present week.

B = Tablet for the next week.

Week = Monday to Sunday inclusive.

Simple quantitative measurements were made on Thursdays in the women's ward and on Fridays in the men's ward : these observations always began at 2.30 p.m. The measurements consisted of:-

1. The measurement of the strength of the grip using a mercury column dynamometer

A modified sphygmomanometer bag was connected to a mercury manometer and the bag was pumped up to a pressure of 60 mm.Hg. The patient was then instructed to squeeze the bag as forcibly as possible. The rise in the mercury column was noted and this was taken as a measurement of the strength of the grip. Three attempts were made by the patient and the highest reading was recorded.

2. The amount of active and passive movement of the neck (full flexion : full extension)

This was measured by asking the patient to perform full flexion and full extension of the cervical spine. When these movements were performed the distance between the external occipital protuberance and the tip of the 7th cervical spine was measured. The difference between the two readings was regarded as the total flexion-extension movement of the neck.

3. Ability to write

This was tested by asking the patient to write his name (and in some cases the date) and finally to draw a circle and a spiral.

In /

In some patients the time taken to walk a given distance was noted; and in a few others cinematographic records were made of the patient's attempts at feeding, or while the patient tried to rise from a chair, or tried to walk.

Tremor was observed and assessed visually, as the use of mechanical methods was impracticable when a sufficiently large number of patients was being studied simultaneously. Rigidity was measured by the observer's performing passive movements of the joints, especially the elbow joint.

The nursing sister in charge of the patients recorded daily on the proforma provided, the patient's ability to swallow (as good, fair or poor), the external evidence of sialorrhoea (as +, ++ or +++), ability to dress, ability to walk, the number of falls per day, the number and severity of crises (oculogyric and sweating), the type of sleep (normal, noisy or disturbed). In addition to the ward sister's records, the physician (G.O.) observed the patients daily and any significant changes were recorded independently. Soon after the trial began it was found that the proforma was not comprehensive enough; further data was required regarding the patient's ability to rise from a chair, ability to feed himself, and his mental state. These points received special consideration by the physician. At the end of each week a summary of the patient's condition was recorded.

Most of the patients on this trial were already receiving benzhexol /

hexol (Artane). Before the trial was begun all were placed on 15 mg. of benzhexol daily and this was gradually reduced over a few weeks to 5 mg. daily. During this period they received some training in the tests which have been described above. When they had received 5 mg. of benzhexol daily for one week, the clinical trial was started.

Second type of Study:

To determine the nature of the pharmacological action and the duration of its effects.

11 patients were selected for this study. Later the number was reduced to 8, as 2 patients suffered from tremor severe enough to prevent their applying sustained pressure on the sphygmomanometer bag; and the other patient was withdrawn from the group because there was only slight weakness of his voluntary muscles.

Three types of active tablets were used: orphenadrine, benzhexol and UK. 738 (Sandoz). The patients also received placebo tablets for control purposes.

Method

This was an "acute" study. On the day before starting the experiment, the patient received the last dose of his usual tablets at 12 noon; and at 6 p.m. he received the placebo. At 9.30 a.m. the /

the next morning (the day of the experiment), measurements were made and recorded and the tablets were given with a copious draught of fluid. Measurements were recorded hourly. Observations were made on the strength of the grip, the amount of active extension-flexion movement of the neck, the degree of rigidity and tremor (using the plus system), the amount of salivation (by observing the amount of dribbling and the degree of moistness of the mouth, especially of the tongue), the heart rate (apex beat) and the size of the pupils. Estimation of the size of the pupils was later abandoned as it proved to be impracticable to standardise the conditions (amount of daylight etc.) under which the observations were made. During the periods of observation, the patients were seated in comfortable chairs and were instructed not to walk about the ward (except to use the lavatory). They were allowed to read and to have lunch at the usual time. The patients were not told what drugs they were having but the objectives of the experiment were explained in general terms.

RESULTS

1. Double Blind Trial

In the final assessment, the therapeutic value of each drug was graded as Satisfactory, Fair or Poor. The results obtained for each type of tablet are shown in Table 14. They were regarded as satisfactory in 62.5% of the patients who received orphenadrine (Disipal), whereas "UK. 738" produced a satisfactory result in only 20.8% of the patients; and none of the patients received any benefit from taking the placebo. "UK. 738" gave poor results in 37.6% of patients and orphenadrine in 8.4%.

Drug	Satisfactory	Fair	Poor
Orphenadrine "Disipal"	62.5%	29.1%	8.4%
"UK. 738"	20.8%	37.6%	41.6%
Placebo	0%	0%	100%

TABLE 14: Results of the Drug Trial

Strength of the grip

The strength of the grip was significantly increased in 15 patients /

patients (62.5%) (Table 15) when they were on active drugs compared with their performance on placebo tablets. Orphenadrine was usually the most effective treatment. In this group of patients the percentage increase for both hands was 43% and 27.7% for orphenadrine and UK. 738 respectively (Table 17). It is of interest to note that the beneficial effect of these drugs on the power of grip was sometimes confined to one hand - usually on the weaker side.

Extension-flexion movement of the neck

The overall percentage increase in the active extension-flexion movement was 32% and 15% for orphenadrine and UK. 738 respectively. When the comparison is restricted to the 15 patients who showed significant increase in the strength of the grip, the benefit amounted to a 50% improvement following orphenadrine and 25% in the case of UK. 738 (Tables 17 and 18). The range of passive movement showed no significant difference between the effects of the placebo and active drugs. This result is accounted for partly by the fact that assessments which depend on passive movement of the neck turned out to be unreliable under conditions of clinical practice, and this test or measurement is not recommended.

Writing

20 patients were able to write but 5 of these (4 men and 1 woman) were unable to complete the writing because of the curious phenomenon of /

Name	UK. 738 Placebo				"Disipal" Placebo				UK. 738				"Disipal"			
	Grip Right	Grip Left	Neck Active	Neck Passive	Grip Right	Grip Left	Neck Active	Neck Passive	Grip Right	Grip Left	Neck Active	Neck Passive	Grip Right	Grip Left	Neck Active	Neck Passive
Cairney	23	-	1.9	4.4	32	-	2.0	3.5	45	-	2.2	4.9	64	-	2.6	4.4
Gilmour	113	119	3.7	6.4	111	108	4.5	7.1	98	123	4.0	7.8	116	151	4.7	8.1
Austin	96	116	3.5	6.5	110	110	4.5	6.2	128	133	5.1	7.0	120	144	6.5	8.5
Patterson	66	43	3.0	7.1	96	50	2.5	6.0	120	83	4.3	6.9	116	92	5.1	7.4
Hughes	118	168	8.0	10.0	84	94	6.8	8.0	201	186	7.3	9.4	220	172	8.0	9.0
McManus	55	45	1.7	5.5	62	63	1.4	5.1	50	50	2.2	6.0	73	80	4.0	6.8
McLaren	65	68	5.6	8.0	60	72	5.2	7.6	99	97	6.4	8.0	116	108	6.5	8.0
Sandler	200	-	2.0	-	200	-	1.8	-	240	-	2.5	-	240	-	3.5	-
McMillan	8	22	-	-	15	25	-	-	33	34	-	-	45	37	-	-
Cadden	58	128	3.5	6.0	-	-	-	-	138	185	3.2	6.0	160	178	4.8	7.3
Pratt	88	28	1.4	-	104	36	1.9	-	143	39	2.1	-	168	51	3.0	-
Hay	-	100	3.0	6.5	-	91	2.8	6.5	-	126	3.4	7.0	-	153	3.6	6.1
Hannan	94	136	4.0	5.5	64	94	4.0	6.0	142	152	3.8	6.0	115	145	5.5	7.2
Power	83	90	3.5	5.3	106	126	4.0	6.0	126	126	4.0	6.5	154	141	5.0	6.5
McIntyre	191	60	4.3	-	206	61	4.7	-	-	-	-	-	222	106	5.0	-

TABLE 15. Strength of grip (mean values) and range of active neck movement (mean values) in 15 patients showing differences which are highly significant. Range of neck movements is measured in centimetres.

Name	UK. 738 Placebo				"Disipal" Placebo				UK.738				"Disipal"			
	Grip Right	Grip Left	Neck Active	Neck Passive	Grip Right	Grip Left	Neck Active	Neck Passive	Grip Right	Grip Left	Neck Active	Neck Passive	Grip Right	Grip Left	Neck Active	Neck Passive
Bissett	101	68	2.6	5.6	82	50	2.2	5.3	88	59	2.6	3.6	94	64	3.5	5.7
McLister	88	58	2.6	4.5	68	51	3.0	6.7	93	63	3.4	6.3	88	70	4.0	7.0
Lant	240	39	3.3	7.5	233	38	3.2	6.9	230	28	4.4	7.1	240	53	6.8	8.5
Bunyan	148	132	6.5	8.0	170	140	5.5	7.5	193	159	6.0	7.4	194	147	5.9	7.4
McCaherty	180	231	7.3	9.0	173	226	7.3	9.0	208	240	7.7	8.9	168	225	7.8	9.0
Bell	240	240	10.0	-	240	240	10.0	-	240	240	10.0	-	226	240	10.0	-
Wyper	240	200	5.8	8.2	240	205	5.5	8.0	240	234	5.8	7.7	240	225	6.4	8.4
McCartney	240	-	3.7	-	220	-	3.0	-	186	-	4.0	-	240	-	5.7	-

TABLE 16. Strength of grip (mean values) and range of active neck movement (mean values) in the other 8 patients showing differences which are regarded as not significant.

N.B. 1. 1 patient who lapsed into catatonic stupor in the second week of the trial was not included.

2. Range of neck movement is measured in centimetres.

Indices of Measurement	Placebo (UK.738)	Placebo (Disipal)	UK.738	Disipal
Power of grip (right hand)	89.9	95	119	137
Power of grip (left hand)	85.1	77.7	111.1	121.1
Active neck movements (in cms.)	3	3.2	4	4.8
% increase over Placebo (right hand)	-	-	25%	44%
% increase over Placebo (left hand)	-	-	30.5%	42%
% increase over Placebo (active neck movements)	-	-	25%	50%

TABLE 17. Strength of grip and range of active neck movements in 15 patients showing differences which are highly significant (mean values).

Indices of Measurement	Placebo (UK.738)	Placebo (Disipal)	UK.738	Disipal
Power of grip (right hand)	124	122	144	155
Power of grip (left hand)	103.7	99	124	125
Active neck movements (in cms.)	4	4	4.6	5.3
% increase over Placebo (right hand)	-	-	16.1%	25%
% increase over Placebo (left hand)	-	-	20%	20%
% increase over Placebo (active neck movements)	-	-	15%	32%

TABLE 18. Strength of grip and range of active neck movements in all patients studied (mean values).

of akinesia. At some point in the act of writing, movement stops - often in the middle of a simple word; and the pencil point remains in contact with the paper for an indefinite time - two minutes or more. In such circumstances patients usually had to abandon the attempt to continue writing. Figures 34, 35 and 36 illustrate this phenomenon in the 5 patients affected. This form of apraxia occurred while the patients were on placebo tablets and in one patient who was receiving the drug UK. 738; it was never seen while the patients were on treatment with orphenadrine.

Patient's ability to feed himself

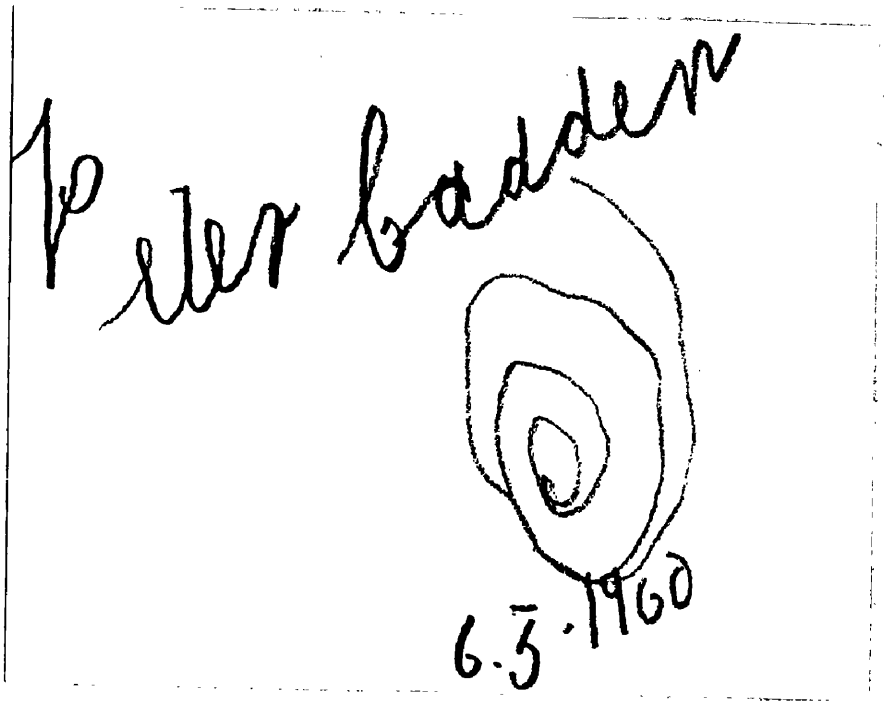
16 patients were unable to feed themselves whilst they were taking placebo tablets. The disability was abolished in 4 of them by giving UK. 738 and in 12 who received orphenadrine.

Rigidity and tremor

Only 9 of the 24 patients (37.5%) benefitted by an appreciable reduction in the degree of rigidity by giving potent drugs. In 10 (41.6%) however, the administration of placebo tablets resulted in gross aggravation of the tremor. Orphenadrine was much more effective than UK. 738 in relieving rigidity and tremor.

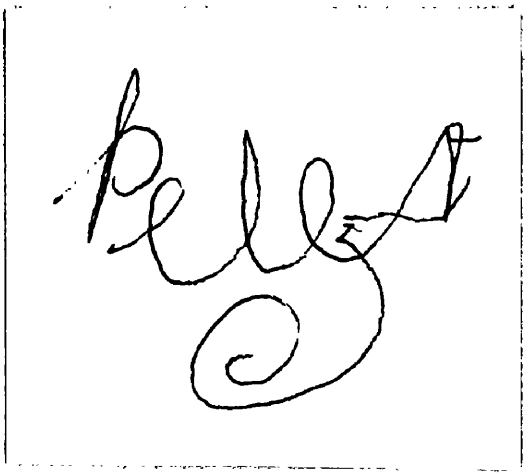
Sweating

The value of active anti-Parkinson drugs including benzhexol in preventing /



(a)

(b)



(c)

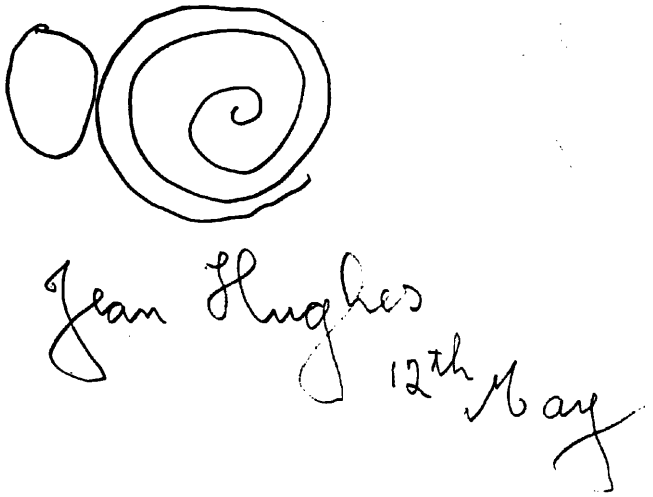
Fig. 34.

Patient's handwriting while on various kinds of drug therapy.

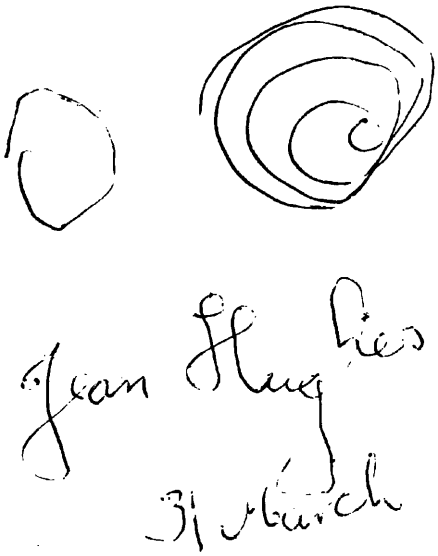
(a) Orphenadrine (100 mg. t.d.s.)

(b) "UK. 738" (4 mg. t.d.s.)

(c) Placebo (2 tabs. t.d.s.)



(a)



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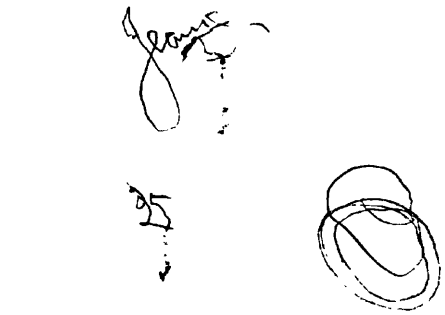


(c)

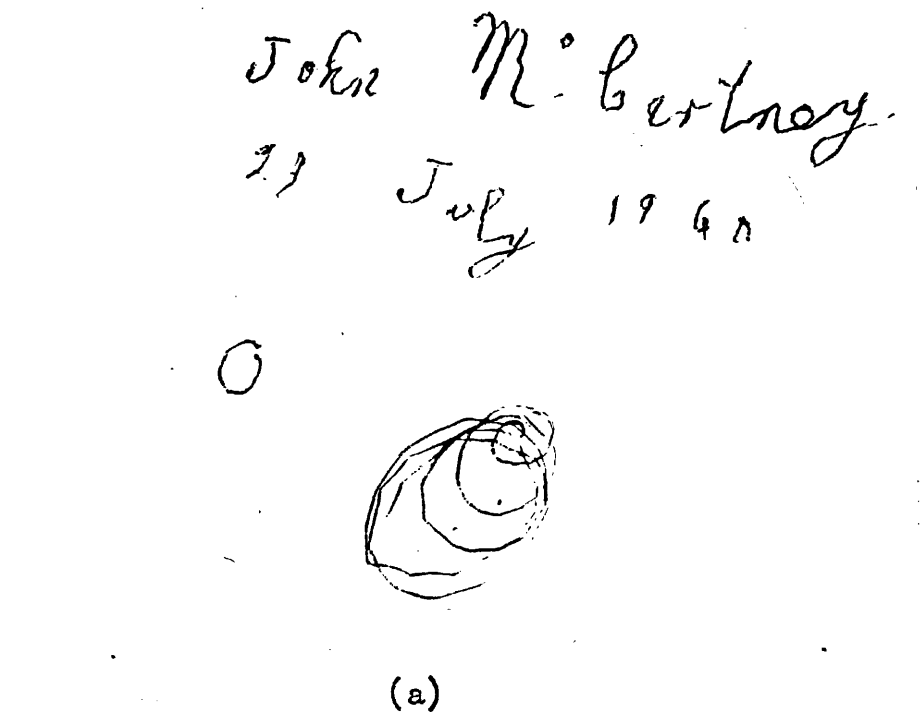
Fig. 35.

Patient's handwriting while on various kinds of drug therapy.

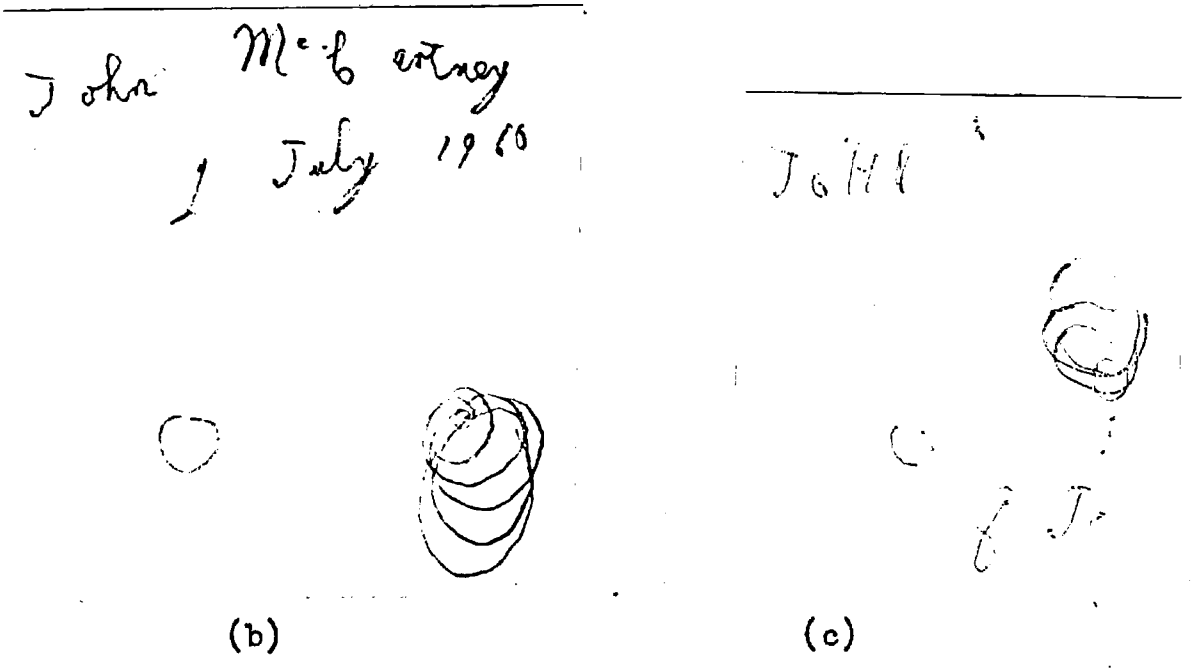
(a) Orphenadrine (100 mg. t.d.s.)

(b) "UK. 738" (4 mg. t.d.s.)

(c) Placebo (2 tablets t.d.s.)



(a)



(b) (c)

Fig. 36.

Patient's handwriting while on various kinds of drug therapy.

(a) Orphenadrine (100 mg. t.d.s.)

(b) UK. 738 (4 mg. t.d.s.)

(c) Placebo (2 tablets t.d.s.)

preventing excessive sweating was confirmed. During this trial 5 patients who had hitherto not complained of excessive sweating were greatly inconvenienced by this disability while receiving only the placebo tablets. The excessive sweating was worse at night time. Before the clinical trial 2 patients suffered from recurring and severe attacks of sweating crises requiring treatment with intravenous sodium phenobarbitone (Onuaguluchi, 1961) as described in Chapter III of this Thesis. One of them (Case 4) was free from sweating crises while receiving "UK. 738". Judged by the criteria listed below, "UK. 738" was the drug of choice for this patient: swallowing was regarded as good during this period, whereas it was graded as "fair" while he was receiving orphenadrine and "poor" when given only placebo tablets. This patient was accordingly treated with "UK. 738" from the time of the clinical trial - a period of 10 months, and he has continued to do well. On one occasion, however, when "UK. 738" was temporarily out of stock, he was placed on orphenadrine 100 mg. thrice daily. He was not informed of the change of treatment. Within a few hours he was flushed and began to sweat profusely; and swallowing became much more difficult. In a few days, treatment with "UK. 738" was resumed and there was an immediate improvement.

Oculogyric crisis

The drugs benzhexol, orphenadrine and "UK. 738" do not seem to have any significant effect on the frequency and severity of oculo-

gyric /

oculogyric crises. Only 2 of the 11 patients (C. Bun and J. Pat.) who suffer from oculogyric crises experienced a definite reduction in the frequency and perhaps the severity of the crises when the patients were receiving orphenadrine. No significant difference was noted with "UK. 738" (Table 19).

Drowsiness

7 of the 24 patients were very drowsy while taking placebo tablets (an effect interpreted as the result of withdrawing active therapy) and 2 of them while taking "UK. 738". In one patient (case 9) receiving placebo tablets, deterioration was complicated by catatonic stupor and he had to be roused by repeated intramuscular injections of "UK. 738" in doses of 2 mg.

Mental depression

Signs of depression were noted in 15 of 24 patients receiving placebo tablets, and also in 6 patients treated with "UK. 738". None of the patients were depressed while under treatment with orphenadrine. On the contrary, orphenadrine often abolished depression rapidly and sometimes produced some degree of euphoria. One patient who enjoyed knitting became tearful and lost interest in her pastime while she was on placebo therapy, but about 24 hours after receiving orphenadrine said: "I feel like flying": and this was in spite of the fact that at that time the physical accompaniments of the post-encephalitic syndrome /

No.	Name	"Disipal"	"UK.738"	"Disipal" Placebo	"UK.738" Placebo
1.	A.Bis	0	3	0	3
2.	R.Pra	1	1	2	3
3.	A.Hay	0	0	3 in 8 days	0 in 4 days
4.	J.Pat	2	5	6	6
5.	M.McL	4	3	5	2
6.	C.McM	3	3	6	2
7.	M.Gil	3	4	4	4
8.	C.Bun	0	1	2 in 4 days	5 in 5 days
9.	T.Pow	1	0	1 in 7 days	0 in 3 days
10.	R.Cai	0	2	0 in 4 days	2
11.	P.Cad	0	2	1 in 3 days	0 in 7 days

TABLE 19: Frequency of oculogyric crisis in each patient during the drug trial. Except where indicated the numbers stand for the frequency in 21 days.

syndrome were only slightly relieved. Table 20 shows the various clinical manifestations of depression in these 15 patients.

Number of premature stoppages of drug therapy

There was premature stoppage of drugs (i.e. stoppage of a drug before the patient has taken the drug for three weeks) on 32 occasions in 14 patients. At the conclusion of the investigation, when the pharmacist's chart was made available, it was discovered that on 26 occasions, these patients had been receiving placebos, on 5 occasions "UK. 738," and on only one occasion during orphenadrine therapy.

SIDE-EFFECTS

Orphenadrine

2 patients (men) complained of difficulty in starting the act of micturition. There was, however, no retention of urine. Three patients had involuntary jerky movements (myoclonus) of the limbs, but in 2 of these patients this effect passed off as therapy continued. One patient complained of dizziness about 1-1½ hours after taking the tablets. Another patient complained of nervousness ("jittery") about 1 hour after taking orphenadrine. Two patients had bleeding episodes during orphenadrine treatment. This was possibly a coincidence. One of them suffered from a hiatus hernia with oesophageal ulcers. The other patient had acute erosion of the gastric /

No.	Name	Drug	Manifestations of depression
1.	C.Bun	Placebos	Very weepy, poor appetite, nausea and vomiting.
2.	M.McC	Placebos	Dull; uninterested in her surroundings.
3.	J.Bel	Placebos	Dull. Complained of difficulty in changing his thought and even in the direction of his gaze from one object to another.
4.	H.Lan	Placebos and "UK.738"	Very emotional; weepy.
5.	T.Pow	Placebos and "UK.738"	Disinclined to leave his bed and go to the day hall. Poor appetite.
6.	A.Hay	Placebos	Poor appetite; vomiting.
7.	C.Han	Placebos	Wants to stay in bed. Dull. Not reading (normally he reads a great deal).
8.	C.McM	Placebos and "UK.738"	Weepy. Lost interest in her usual hobby (knitting).
9.	J.Hug	Placebos	Disorientated, hallucinations; said she saw goldfish. Dull; appetite poor.
10.	M.Aus	Placebos and "UK.738"	Very weepy, appetite poor.
11.	R.Cai	Placebos	Dull and uninterested in her surroundings. Very poor appetite; nausea and vomiting.
12.	N.San	Placebos	Dull; poor appetite.
13.	R.Pra	Placebos and "UK.738"	Moaning ++ even during the night. Dull. Wants to stay in bed all the time in spite of the fact that his gait was still quite good.
14.	P.Cad	Placebos	Unwilling to leave his bed. Dull: appetite very poor - refusing his meals, vomiting +.
15.	J.McI	Placebos	Dull. Unwilling to leave his bed. Delusional (paranoid type).

TABLE 20: Manifestations of depression in 15 of the 24 patients while on various forms of therapy during the drug trial

gastric mucosa with severe melaena; his condition necessitated partial gastrectomy, but the bleeding point was not found at operation. In this patient, haemorrhage began about 15 minutes after dental treatment (scaling and polishing). Five patients complained of a burning sensation in the throat but this was not unbearable.

"UK. 738"

No side-effects were noted. The drowsiness seen in 2 patients might be regarded as a side-effect, but it was more probably a sign of inadequate drug therapy; the occurrence of drowsiness was even greater in patients receiving placebo tablets.

2. RESULTS IN THE SECOND TYPE OF STUDY

Figure 37 shows that peak action (as judged by the effect on muscle) attributable to orphenadrine and benzhexol occurs in about 2 hours and in 2 to 3 hours respectively. The period of maximum activity due to "UK. 738" was less easily defined. Orphenadrine is probably more rapidly excreted from the body than is benzhexol as judged by the duration of therapeutic effects. Figure 38 shows the mean dynamometer readings in 8 patients after taking orphenadrine, benzhexol, "UK. 738" and placebo tablets. In the individual patient, the effect of orphenadrine may last up to 6 hours but the most effective period is between 2 to 4 hours after taking the tablet. In this type of acute experiment for the assessment of drug action, extension /

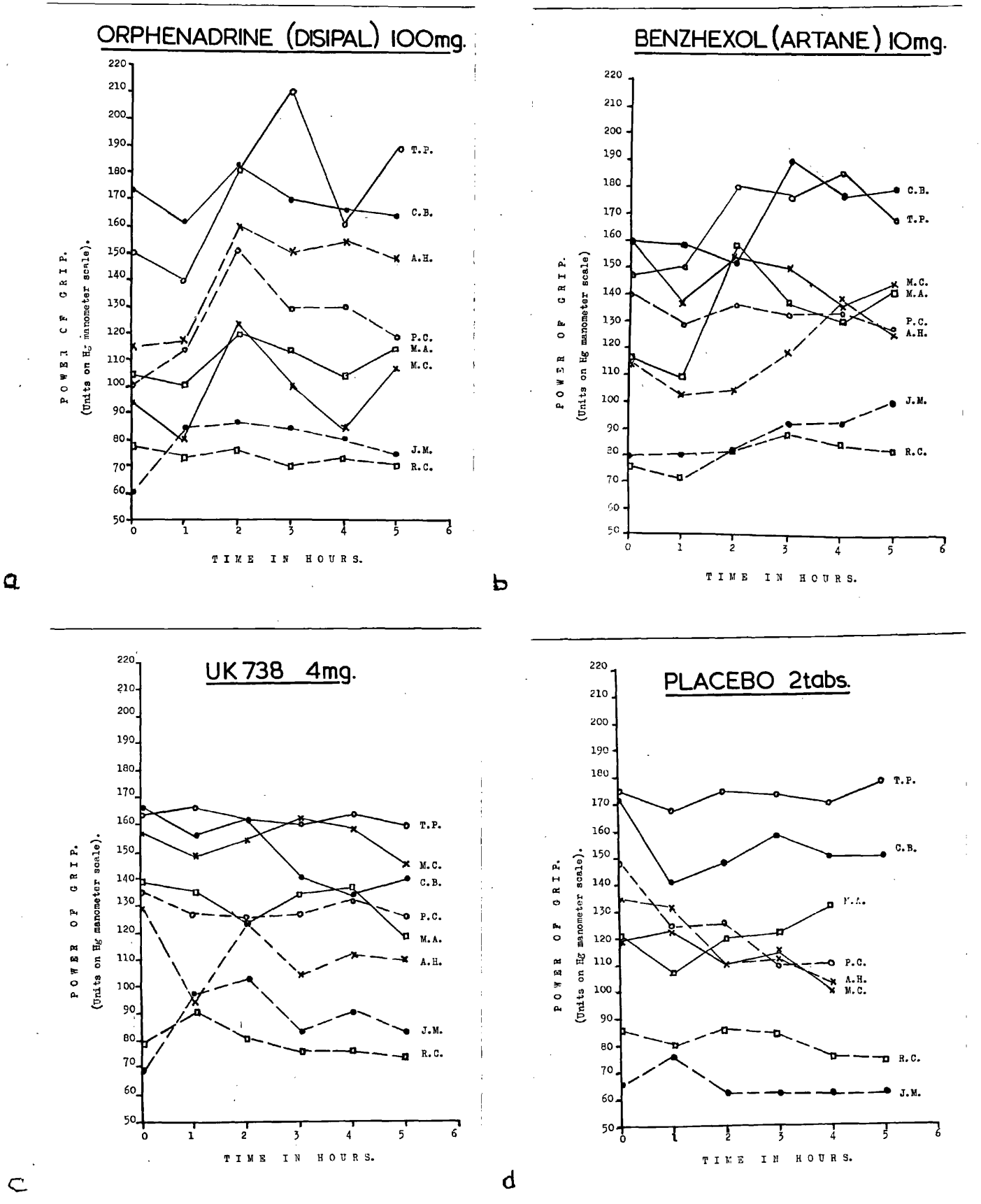


Fig. 37 a,b,c,d. The effect of 100 mg. of orphenadrine, 10 mg. of benzhexol, 4 mg. of UK. 738 and 2 placebo tablets on the strength of grip in 8 patients.

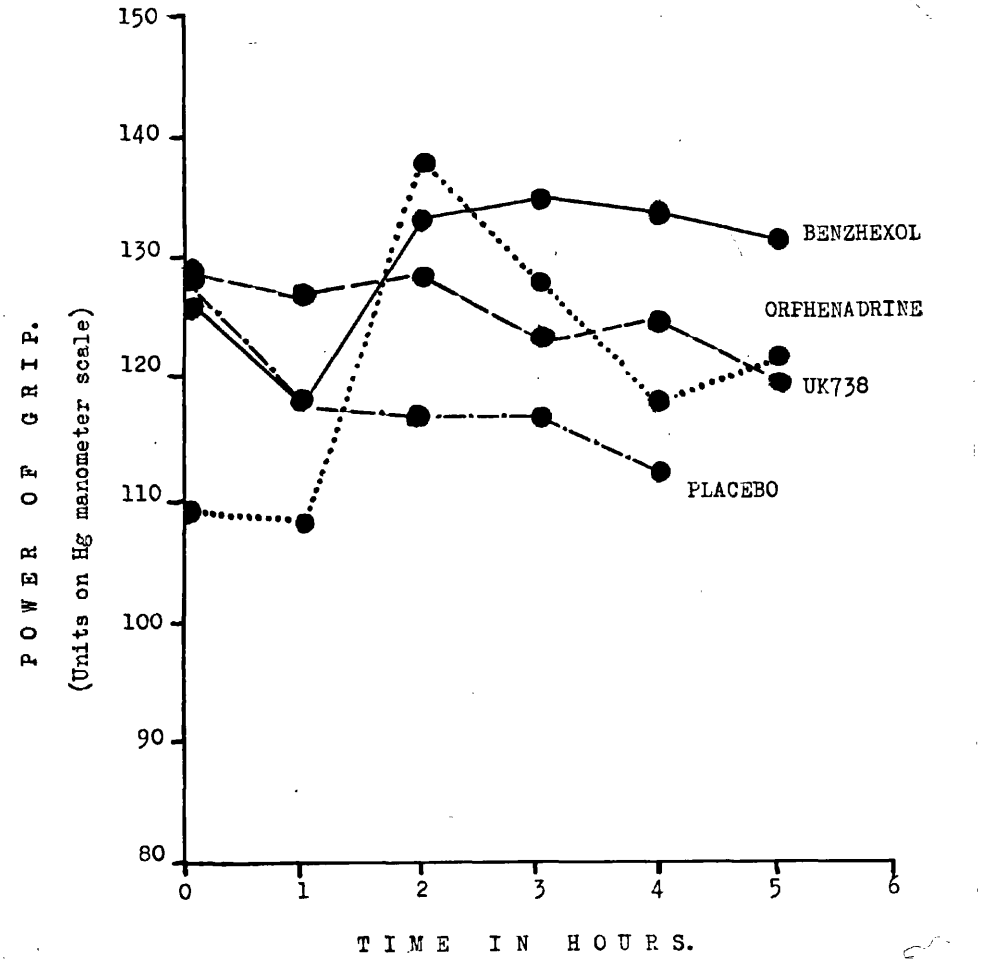


Fig. 38. Mean dynamometer readings in 8 patients after administration of 100 mg. of orphenadrine, 10 mg. of benzhexol, 4 mg. of UK. 738 and 2 placebo tablets. Each point represents mean of at least 12 tests.

extension-flexion movements proved to be of no value.

From the comparative study of antisialogogue effect it is clear that activity usually started in the first hour but may be delayed until the second hour after oral administration of orphenadrine, benzhexol and UK. 738. Peak activity occurred two to three hours after taking the tablets; the antisialogogue activity lasted for another two to three hours. It appears that of the three drugs, benzhexol has the greatest antisialagogue activity; orphenadrine is appreciably less active. In making such comparisons, however, it must be emphasised that they refer to quantities of the various drugs which have become standardised as the doses usually employed in clinical practice, namely, benzhexol 10 mg., orphenadrine 100 mg., and UK. 738 4 mg.

DISCUSSION

The results of the drug trial show that both orphenadrine and UK. 738 have useful pharmacodynamic actions in patients suffering from post-encephalitic Parkinsonism. Orphenadrine is probably about 3 times as effective as UK. 738. This bald statement is of some value to the practitioner who must decide, with the help of research reports, which of the available drugs is most likely to produce the best therapeutic effect. However, the relative merits of a group of potent drugs cannot always be fully defined by means of such comparisons. To some extent the response of a patient to the action of a drug is an individual characteristic and only trials on a particular patient will decide which drug is best for him. Hence a drug may be a useful addition to those already employed in the treatment of Parkinsonism, even though it gives satisfactory results in only 20% of the patients who receive it.

The relief of depression by orphenadrine is very striking. This confirms the views of others (Doshay and Constable, 1957) and recently (Robinson and Dick, 1960). As to the pathogenesis of depression in this disease, it is certainly not secondary to physical disability, as a number of very "disabled" patients were not depressed. Further, various accompaniments of depression such as loss of appetite, nausea, vomiting, delusions and hallucinations were often present in these depressed patients. It is noteworthy that such disabilities as difficulty /

difficulty in swallowing, speech disturbances, and incontinence of urine, which are considered as contra-indications to surgical operations on the globus pallidus and thalamus (Cooper et al, 1958; Gillingham et al, 1960) may be greatly alleviated by adequate treatment with the potent drugs now available.

One interesting phenomenon in Parkinsonism which has hitherto received very little attention is akinesia. This phenomenon is a very complex one but can be described as a liability to sudden arrest of voluntary movement while carrying out purposive actions; the limb or limbs are "frozen" unexpectedly and unpredictably. It has been demonstrated in the handwriting of 5 patients when they were taking placebo tablets. It is of interest that apraxia of handwriting such as was seen in these patients has been described as a sign of frontal lobe lesions (Meyer and Barron, 1960). In such patients there is usually apraxia of the gait and there is a grasp reflex. Only 3 of the 5 patients with apraxia of handwriting were able to walk before the trial was begun. Two out of these three had apraxia of gait in conjunction with apraxia of writing; but only one patient had positive grasp reflex by the conventional method of testing. It must be mentioned that very great difficulty in releasing a grasped object was experienced by 4 patients in this series during placebo therapy. Three of them (2 of whom also showed apraxia of handwriting) had acquired the habit of holding their noses, and because of the apparent inability to relax their grasp two of them nearly suffocated themselves; they /

they developed cyanosis which was sufficiently severe to necessitate the administration of oxygen.

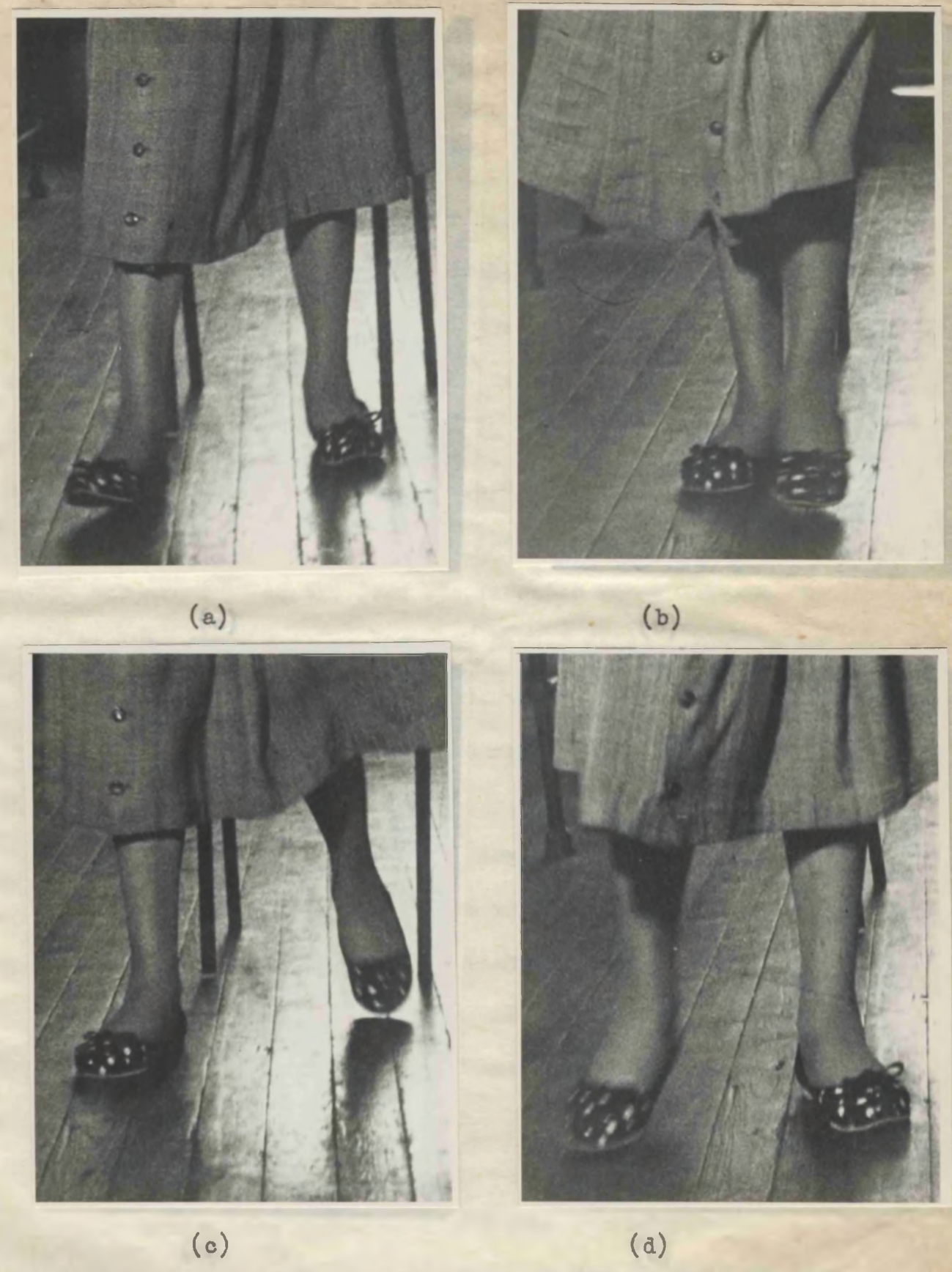
The gait may also be affected by akinesia. Figures 39 and 40 are taken from cinematographic records of a patient's attempt at walking during treatment with placebo tablets (Fig. 40) and also while receiving orphenadrine tablets (Fig. 39). During placebo therapy she was unable to walk and in Fig. 40 she had not taken one step forward after 44 seconds. In contrast to this, during orphenadrine therapy the gait was easy. This is obvious in the cinematograph film and can be discerned even in a series of "stills" taken from the film. Disturbances of gait (excluding festination) which are seen in Parkinsonism are probably due to the following factors:-

(1) Difficulty in initiating the movement - the feet seem to be held bound to the ground (akinesia).

(2) Increased rigidity - which is probably also responsible or associated with (1). The increased rigidity causes the gait to be slow although in one patient (R.Pra., Case 1), in spite of marked increase in the degree of rigidity and the presence of apraxia of handwriting during times of placebo therapy, there was no difference in the time taken to walk a given distance (twice the length of the ward) during all forms of therapy.

(3) Retropulsion - which prevents propulsion and usually causes the patient to fall.

(4) /



(a) (b)

(c) (d)

Fig. 39. Case 3. "Stills" from cinematographic study of the patient's attempt at walking while receiving orphenadrine 100 mg. t.d.s. (a) Start. (b) After 0.44 sec. (c) After 0.88 sec. (d) After 1.72 sec.

(a)

(b)

(c)

(d)

Fig. 40. Case 3. "Stills" from cinematographic study of the patient's attempt at walking while receiving placebo tablets. (a) Start. (b) after 5 sec. (c) After 11 sec. (d) After 16 sec. Note the patient has yet to take a single step forward.

(4) Weakness and lethargy - which in combination with rigidity and akinesia makes the patients easily fatigued when walking.

Another form of akinesia which was observed in these patients is seen when patients attempt to feed themselves. This phenomenon was seen in its purest forms in two patients. One patient (Case 2) was unable to feed herself when she was receiving placebo tablets because the hand stopped halfway to the mouth and remained there indefinitely. When she was receiving the preparation UK. 738 she was also unable to feed herself. During this period she was able to get food into her mouth but movement of the jaws was arrested while chewing it. During both periods she had to be fed with mashed food. Fortunately her ability to swallow was not affected. Various factors apart from gross deformities of the hands seem to be responsible for the inability to feed oneself:-

(1) Akinesia, whose role has been described.

(2) Increased rigidity, which may make feeding laborious and tiresome. Thus some patients require help during the latter half of the meal. If they are allowed to continue on their own unaided, it has been noted that it can take well over 90 minutes before the patient is able to finish a simple meal.

(3) The flexed position of the neck, if very marked and relatively fixed, is another factor which is of some importance.

(4) /

(4) Tremor is another factor, which even when of moderate severity, may prevent the patient from feeding herself, especially with liquids; tea, soup, etc.

Schwab, England and Peterson (1959) have also studied the problem of akinesia in Parkinsonism although they used a different approach. They state that akinesia in Parkinsonism includes the following manifestations:

(1) Constant awareness of fatigue;

(2) Difficulty in shifting from one motor contraction pattern to another;

(3) Inability to complete tasks and hence others are never begun.

They made the point, which was also observed in the present series, that most of the patients lose their normal alertness and may fall asleep while watching television programmes which are sufficiently interesting to hold the attention of other post-encephalitics. They considered that akinesia is unrelated to tremor but is probably related to rigidity; and this was the conclusion reached in the present series. They found that the E.E.G. was usually abnormal. This point has been mentioned in the section dealing with electroencephalography in Parkinsonism. These workers found that in severe cases the usual drugs were ineffective, and they regarded surgery and chemopallidectomy to be contra-indicated and proposed that amphetamine and strychnine should be prescribed for these patients. The present investigation has shown, however, /

however, that orphenadrine is often effective in relieving moderately severe forms of akinesia; and it may be of value even when the symptoms are severe. Although the present investigation did not include a clinical trial of amphetamine in the treatment of Parkinsonism, it is justifiable to draw attention to the severe restlessness which can be produced by amphetamine and which may be very disturbing to the patient.

Methods of Assessment of Drug Therapy

In order to evaluate the merits of any form of treatment it is often essential that improvements in the patient's condition should be measurable objectively. The complexity of such measurements may reduce their value as they can then only be made in special centres. An attempt should therefore be made to devise simple and easy techniques in quantitative measurement so that they can be used in any hospital where patients suffering from Parkinsonism are cared for.

Rather surprisingly, the value of quantitative objective measurement in the assessment of drug therapy in Parkinsonism has been doubted. Gillhespy and Ratcliff (1956) declared that the criteria for judging improvement must be based on what are necessarily subjective phenomena. Schwab and Leigh (1949) used various objective tests which included E.M.G. studies, handwriting, and finger-thumb rates and found that only the finger-thumb rate was of any value. They therefore came to the conclusion that subjective accounts of well being, and relatives' /

relatives' report of the patient's greater ability to carry on with household duties were more reliable than objective measurements. Merrit (1954) quoted by Agate, Doshay and Curtis (1956), in discussing this problem said: "The beneficial effects of medical therapy seem largely to be of a subjective nature since efforts thus far to measure objectively any reduction in rigidity and tremor yielded negative results".

On the other hand, Berkowitz and Alverman (1952) found no evidence that a patient's subjective evaluation of his condition reflected changes in his objective motor and mental efficiency. They concluded that objective tests are useful in evaluating improvement in paralysis agitans and are probably more reliable than subjective evaluation. Eliasson and Tejning (1956) claimed from their studies that objective and subjective effects showed a fairly good correlation. Agate, Doshay and Curtis (1956) developed an electronic apparatus capable of measuring the torque exerted on the forearm during extension of the elbow. They found that there was a statistically significant difference between the mean rigidity at the end of a placebo period of at least 3 days' duration and the mean rigidity at the end of 7 days' treatment with drugs known to be clinically potent. With this apparatus they were also able to measure the amplitude of tremor. Webster (1960) using a powerful and highly sensitive turntable that reciprocates on a horizontal plane through an arc of 100^{o} at various speeds claimed to be able to measure rigidity, tremor and muscle strength with some accuracy.

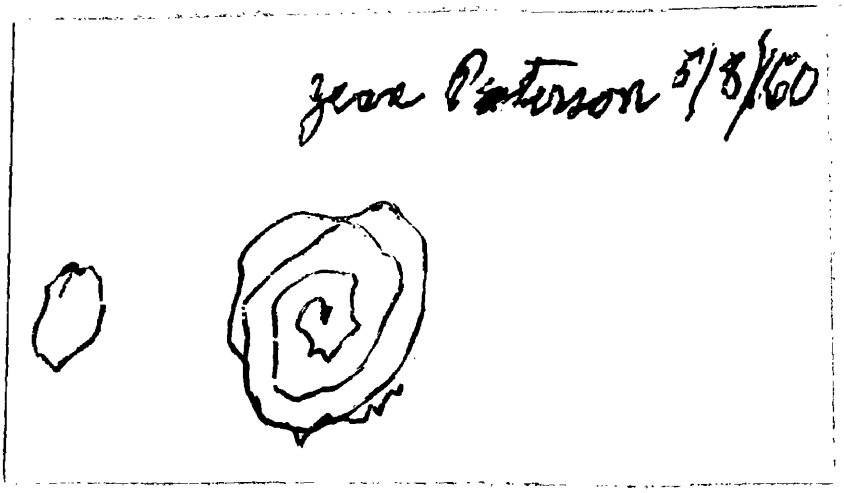
Measurement of Tremor

1. Handwriting

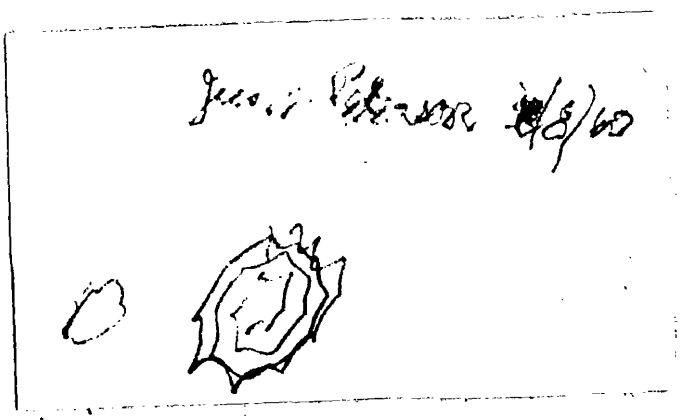
The character of the patient's handwriting is commonly regarded as indicating the severity of his disability due to tremor. In this study, however, it was clear that in a large proportion of patients, tremor was diminished or disappeared altogether from the hand during the act of writing although the other hand continued to shake. This observation is in fact, in keeping with the well known fact that tremor in Parkinsonism is a tremor at rest and disappears or diminishes greatly when voluntary movement is being executed - only to reappear when the movement has been completed. It was possible to demonstrate the degree of tremor by means of the handwriting in a small proportion of patients only (Fig. 41). Such patients usually have moderately severe or very severe tremor or are highly emotional with emotional exaggeration of the amplitude of the tremor. Notwithstanding these observations, there is no doubt that the patient's ability to use a pencil provides a valuable objective test, especially as by this means the phenomenon of akinesia in the form of apraxia of handwriting can sometimes be detected.

2. Use of a lighting device.

This method was used to study tremor in two patients before and after chemopallidectomy. (The set up - Fig. 42 - was devised in collaboration with Dr. J.C. Brocklehurst and the hospital photographer, Mr. P. Waldie). A darkroom is required and the patient is draped in black /



a



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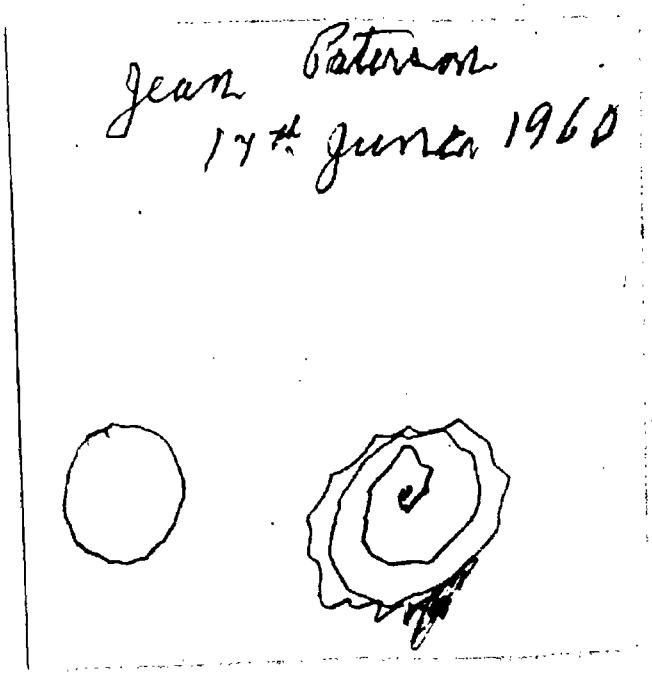

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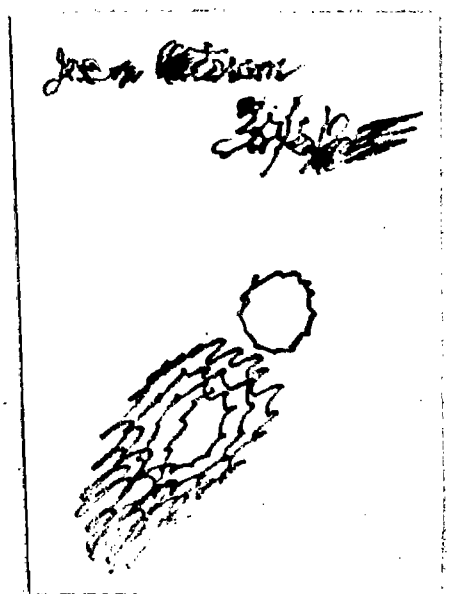


d

Fig. 41. Case 6.

Patient's handwriting while on various kinds of drug therapy.

(a) Orphenadrine (100 mg. t.d.s.)

(b) "UK. 738" (4 mg. t.d.s.)

(c) Benzhexol (5 mg. t.d.s.)

(d) Placebo (2 tablets t.d.s.)

Fig. 42. Apparatus for measuring tremor.

1. Camera.
2. Small hooded electric bulb.
3. Flex connecting bulb to a dry cell battery in patient's coat pocket.
4. Sling of velvet cloth.
5. Cord attaching the sling to a wooden beam above.

black cloth unless he is wearing a dark suit. A small hooded electric bulb is strapped to the dorsum of the hand so that it projects just proximal to the metacarpo-phalangeal joint. The bulb is connected by a flex to a dry cell battery - which is conveniently placed in the patient's coat pocket. The patient's arm is supported as in the diagram by a sling of velvet cloth fixed in place by a strong string attaching it above to a beam fixed to opposite walls in the room. The patient is allowed to settle down for about five minutes. Records are then taken over a period of 15 minutes by exposing the point of light to the photo-sensitive film of a 5" by 4" plate camera 2 feet 3 inches from the patient. A small lens aperture (f.32) is used. Figures 43 and 44 show the records before and after operation. Tremor is assessed by the degree of scatter of the light rays. If the tremor diminishes in amplitude the area of scatter of reflected light is much reduced. As a matter of interest the line traced by the point of light shows quite convincingly that the tremor of Parkinsonism is of the pill-rolling type. The tremor movements take the form of loops even when this is not usually discernible in severe tremors as in the patient whose records were shown in Fig. 44. This method is impracticable when large numbers of patients are to be studied at the same time and it is not therefore a suitable technique for double blind trials described in this investigation. Further, drooping of the wrist may occur during the period of recording, thereby reducing the amount of light (from the electric bulb) passing through the narrow lens aperture. The effect of this is seen in Fig. 44(b).

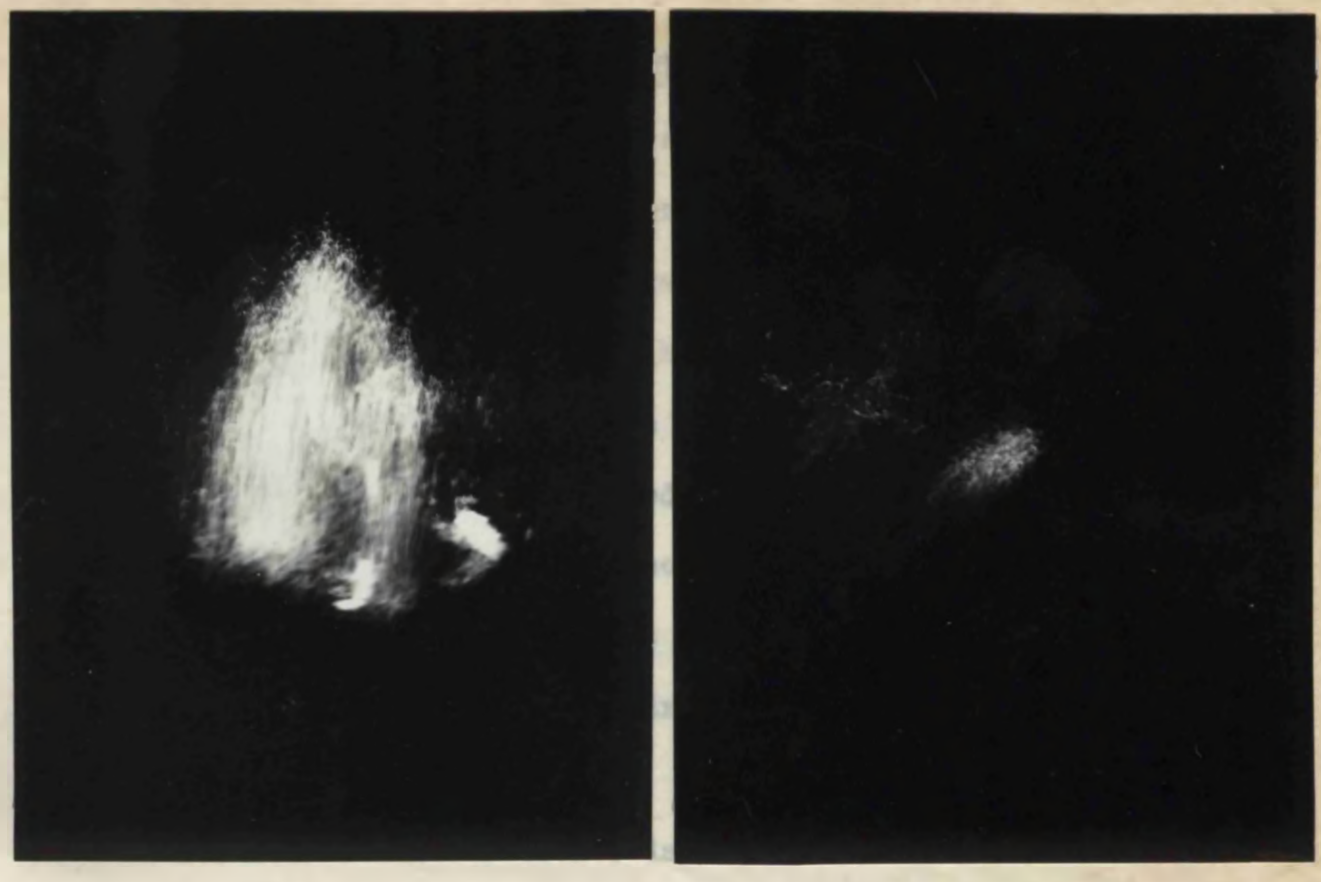
(a)

(b)

Fig. 43. Record of tremor of left hand before and after right-sided chemopallidectomy. Patient aged 55 years and suffering from post-encephalitic Parkinsonism. Record taken over a period of 15 minutes.

(a) Record taken 10 days before operation.
(b) Record taken a year after operation.

Note the marked reduction in the amplitude of the tremor.



(a) (b)

Fig. 44. Record of tremor of left hand before and after a right-sided chemopallidectomy. Patient aged 62 years. Stated to have had encephalitis lethargica in 1920.

(a) Record taken 2 days before operation.

(b) Record 30 days after operation. Each record was taken over a period of 15 minutes.

Note the record (b) is of limited value because of technical faults mentioned in the text but it shows that the amplitude of the tremor has been reduced.

3. The method of Eliasson and Tejning (1956).

In this method, use is made of a light plastic ball: it is fenestrated and the holes are of specified size. The ball is kept loaded by means of a receptacle containing carborundum. The plastic ball is attached to the back of the hand. Tremor of the hand causes the carborundum to be shaken through the holes. The amount of sand (carborundum) lost in a stated period (3 hours) is taken as an index of the degree of tremor. This method is simple and inexpensive. Further, because of the light weight of the apparatus the patient suffers little discomfort and, as already stated, tremor can be measured over a prolonged period of 3 hours. One of the great drawbacks in the quantitative measurement of tremor is the fact that variations occur with such factors as emotional excitement. These variations, though fleeting, may last an appreciable time - measured in minutes. Measurements over long periods is therefore advantageous and should be carried out whenever this is feasible. In my view, clinical assessment of tremor is reasonably accurate but the value of objective quantitative measurement lies in the fact that a permanent record of the tremor is kept and can be compared with greater accuracy with records of tremor at any stage of a study.

4. Apparatus with electronic devices.

Apparatus with electronic devices have recently been used in the measurement of tremor (Agate et al, 1956; Wachs et al, 1960). The apparatuses are said to be highly sensitive but they do not seem to offer /

offer any major advantage over the simple and inexpensive method of Eliasson and Tejning. Wachs and Boshes (1961) listed a number of factors which created artefacts in the tremor tracings using their highly sensitive apparatus (Wachs et al, 1960). These include:-

(a) coughing which gives a high amplitude to the tracing;

(b) fatigue of limb causing the tremor to be irregular in amplitude and frequency and consequently making it impossible to make measurements for long periods.

(c) The height to which the limb is raised affects the amplitude of the tremor although it does not affect its other qualities. As the height of the limb increases the amplitude of the tremor also increases.

5. Other Methods

These include:-

(1) The use of tambour method which in our experience in this unit is highly unsatisfactory as the amplitude of the tremor is often markedly damped down by the inertia in the air column and in the movable parts of the apparatus.

(2) The use of electromyography. This requires the use of intramuscular leads if accurate recording is to be obtained (Wachs and Boshes, 1961). The procedure is therefore painful and may produce artificial patterns purely from nociceptive reaction.

Measurement of Rigidity /

Measurement of Rigidity

Quantitative measurement of rigidity is still difficult, although apparatus devised by Agate et al (1956), Webster (1960), Wachs et al (1960) are said to be reliable. Wachs and his co-workers (1960), however, found that they obtained approximately the same degree of accuracy by clinical assessment (grading as +, ++ etc.). When estimating rigidity, it is essential to remember that in many cases muscle tonus is affected by the rate at which the examiner moves the joint: rigidity apparently increases when passive movement of the joint is rapid. It is therefore essential that the rate of passive movement should be fairly constant, and this also applies when sensitive instruments are being used.

Measurement of Muscle Strength

Although James Parkinson (1817) regarded muscle weakness as one of the cardinal manifestations in "the shaking palsy", clinicians have not paid much attention to this symptom. In the present series, the average strength in the 24 patients studied was less than 50% of that of comparable normal people. Measurement of muscle strength should be a routine procedure in assessing the therapeutic value of drugs used in Parkinsonism. The mercury column dynamometer is preferred to the spring dynamometer as the former is less irksome to the patient. Readings are accurate to about 10 mm.Hg. It should be noted that when muscle power approximates to normal, no increase in power can be expected /

expected from drug therapy; or at least no improvement can be detected by the technique described here. It must be emphasised that a drug or a surgical therapeutic procedure such as chemopallidectomy may considerably reduce the degree of tremor and rigidity but the patient may simultaneously become much weaker. Table 21 is a record of the dynamometer readings of a patient before and after chemopallidectomy. The marked fall in the strength of grip in the first four weeks after operation is demonstrated. His strength was significantly increased when benzhexol was administered. The main disability was tremor: this was dramatically improved immediately after chemopallidectomy but it gradually recurred, reaching its pre-operative state in about eight weeks.

Design of Drug Trial

Before the full scale double blind trial was begun some preliminary studies were carried out using active and placebo tablets of "UK. 738." Excepting one patient who was not receiving any drug (because he had little or no tremor and rigidity) all the seven patients studied received at the beginning of this preliminary study "UK. 738" or its placebo in addition to their usual drug therapy which, in the majority of cases, was benzhexol. In the later stages of the study, however, these drugs were gradually withdrawn in 3 patients so that they received only "UK. 738" or its placebo. The measurements used in this preliminary study were more comprehensive than those used in the full scale /

Period	Highest values Power of grip		Degree of tremor	Degree of rigidity
	Right hand	Left hand		
Before operation (Right sided chemo-pallidectomy).	142	112	Rt. + Lt. ++	Rt. 1 Lt. 2
4 weeks after operation.	90	56	Rt. ± Lt. +	Rt. 1 Lt. 2-
10 weeks after operation.	120	68	Rt. - Lt. ++	Rt. 1 Lt. 2
12 weeks after operation. Received benzhexol 5 mg. t.d.s. for 2 weeks.	134	82	Rt. - Lt. ++	Same
9 months after operation. Still on benzhexol 5 mg. t.d.s.	150	110	Rt. - Lt. ++	Same

TABLE 21: Power of grip, degree of tremor and rigidity before and after chemopallidectomy.

NOTE: the considerable fall in the power of grip after operation. It is surprising however that the power of grip and the degree of tremor of right upper limb was affected by a right-sided chemopallidectomy.

scale double blind trial already reported; they included measurements of the lateral flexion of the spine, and total extension/flexion movement at the ankle and wrist joints.

At least two important points were brought out from the results of this preliminary trial. The first was the fact that placebo therapy can produce a marked improvement in impressionable patients. The patient who was originally on no drug therapy improved on placebo tablets (placebo to UK. 738) and there was no real difference between placebo and active tablets (Table 22). On the other hand, the progressive improvement in the patients' performances between 9.11.59 and 11.12.59, and the increases in the power of grip as the dose of the placebo tablets was being stepped up, might have been due to the fact that the patient was becoming more acquainted with the techniques of the tests. Gillhespy and Ratcliffe (1955) state that about 10% of patients are likely to show this phenomenon, and they suggested that a preliminary study should always be carried out in order to exclude such patients from the main trial. Although this patient was not included in the main trial, no preliminary study was carried out amongst the 24 patients selected for the main clinical trial. This decision is justified on the grounds that most of the patients likely to show marked improvement while on placebo therapy are those with very mild disability; and patients with relatively severe physical disability are very unlikely to show any significant improvement on placebo therapy. Where a study includes a substantial number of patients /

Date	Drug	E.F. Cervical & Lumbar cm.	L.F. Cervical	Grip Right Hand	Grip Left Hand	Maximal flexion P.I.P. index finger Right	Maximal flexion P.I.P. index finger Left
9.11.59	none	13.5	35°	-	-	95°	106°
30.11.59	none	15.2	32°	-	-	98°	108°
11.12.59	"UK.738" placebo ½ tab. daily for 10 days.	17.1	30°	-	-	105°	109°
18.12.59	"UK.738" placebo ½ tab. b.d. for 7 days.	17.4	45°	-	-	104°	102°
29.12.59	"UK. 738" placebo tab. i b.d. for 11 days.	17.4	50°	184	190	104°	110°
26.2.60	"UK. 738" placebo tab. ii b.d. for 4 weeks.	17.9	50°	220	226	105°	106°
8.4.60	"UK. 738" Placebo tab. ii t.d.s. for 6 weeks.	17.9	45°	240	240	105°	106°
20.4.60	"UK. 738" Tab. ii t.d.s. (12 mg.daily for 12 days)	17.0	53°	240	230	108°	107°

TABLE 22: Patient aged 42 suffering from a mild form of Parkinsonism. Results of measurements during double blind trial.

E.F. = Total extension flexion movement.
L.F. = Total lateral flexion movement.
P.I.P. = Proximal interphalangeal joint.

patients with mild disability the method used by Gillhespy and Ratcliffe (1955) (Fig. 45) is recommended but this has the disadvantage that only one drug can be studied at any one trial. If it is planned to assess the therapeutic value of several drugs, then the method described here for the main trial is more useful (Fig. 46). Further, it has the advantage that in three to four months reliable information can be obtained about the relative merits of two to three drugs. In contrast only one drug can be studied in the same period using the method of Gillhespy and Ratcliffe.

The second point of interest in the results of this preliminary study was that no significant difference was noted between the therapeutic effects of UK. 738 and its placebo. This was very puzzling. At first sight the results lent support to the views of Schwab and Leigh (1949) and others - that in the assessment of drug therapy in Parkinsonism objective measurements are of no value. However, consideration was given to the various causes of failure to detect differences in therapeutic effects by quantitative objective measurements:

1. An active drug may not be effective <u>in the dose given</u>.
2. Patients may not be co-operating in the sense that they become careless and fail to give their best performances at all times.
3. The methods used may not be of sufficient sensitivity to detect the differences.
4. Under specified conditions of administration, the drug might /

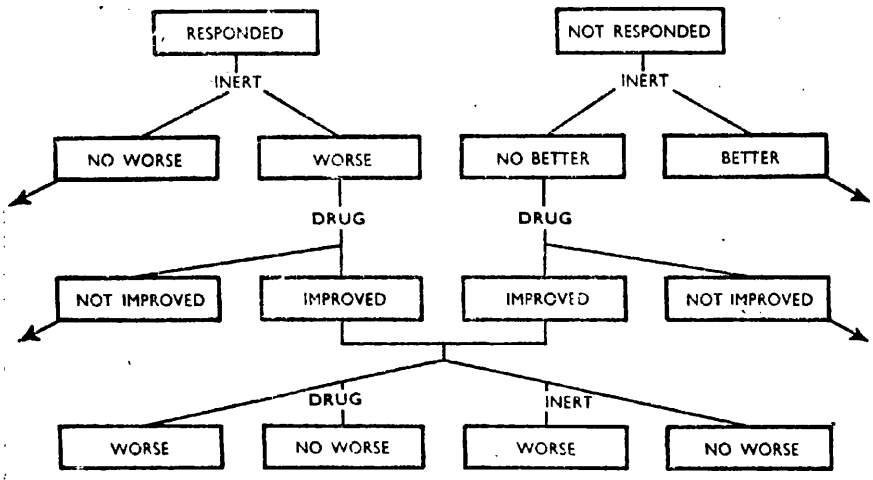


Fig. 45. Illustrates the method used by Gillhespy and Ratcliffe (1955 and 1956) in conducting their drug trial.

From the results of previous treatment patients selected at random are classed as "Responded" or "Not Responded". Both groups are then given placebo tablets for 2 weeks and their clinical condition reassessed. Those from the "Responded" group who are "No Worse" are eliminated from the trial. Those from the "Not Responded" group who are now better are also eliminated. The remaining patients are then treated with the new drug for some weeks and further clinical assessment is made. Those who are "Not Improved" are withdrawn and return to their previous treatment. Those who are improved are divided into 2 evenly matched groups, one group receiving active treatment and the other inert tablets for 2 weeks. At the end of this they are re-assessed and classed as "Worse" or No Worse".

DRUG TRIAL - PARKINSONISM

25A Male	Week Beginning											
	March		April				May					June
	21	28	4	11	18	25	2	9	16	23	30	6
Cadden	R	R	R	S	S	S	V	V	V	P	P	P
Power	S	S	S	R	R	R	P	P	P	V	V	V
McMillan	P	P	P	V	V	V	R	R	R	S	S	S
Hay	V	V	V	P	P	P	S	S	S	R	R	R
Wyper	R	R	R	S	S	S	P	P	P	V	V	V
Hannan	S	S	S	R	R	R	V	V	V	P	P	P
25B Female												
McCaherty	R	R	R	S	S	S	V	V	V	P	P	P
Cairney	S	S	S	R	R	R	P	P	P	V	V	V
McLister	P	P	P	V	V	V	R	R	R	S	S	S
Bisset	V	V	V	P	P	P	S	S	S	R	R	R
Bunyan	R	R	R	S	S	S	P	P	P	V	V	V
Hughes	S	S	S	R	R	R	V	V	V	P	P	P

Fig. 46. Master chart showing order in which drugs were to be given to the first batch of 12 patients in the trial.

might result in a well defined peak period of activity - when the therapeutic value may also be at a maximum. In such circumstances it would be imperative to stipulate the timing of the tests carried out to determine the effect of the drug on muscle power, tremor, etc.

It was thought that the phenomenon of peak activity might be of great importance and this led to the second type of study using "acute" experiments to determine the onset and duration of drug action. The results of the "acute" experimental study serve to emphasise the importance of certain points in the design of clinical trials of drugs used to relieve Parkinsonism. It is well known that, in general, when drugs are given at the usual four-hourly intervals the effects are in some degree uneven; peak periods of pharmacological activity occur and by careful testing, their clinical accompaniments can be identified. It follows that in a clinical trial the time of administration of the drug and the period in which observations are made must be adhered to rigidly; and failure to do so may account for variation in the results obtained by different workers. The main double blind trial described was therefore designed with the possible effects of peak activity in mind.

Other factors affecting the results of quantitative objective measurements in clinical trials

1. The Influence of Emotion: Another factor affecting objective measurements /

measurements in clinical trials in Parkinsonism is the influence of emotion on performances in patients suffering from Parkinsonism. Emotion alters performance and as a result one should try to eliminate all conditions likely to cause emotional variations. Thus the measurements are made at set times and on specified days.

2. Patients Lack of Familiarity with the Procedure of the Objective Tests.

It is essential that before starting the drug trial, the patients must be fully acquainted with the procedure used in the objective tests. A period of two to three weeks should be used to familiarise the patients with the tests, otherwise the performances in the early part of the trial may compare unfavourably with those obtained later, and this spurious improvement will vitiate the results.

Final Assessment of the Therapeutic Value of a Drug

In the final assessment of therapeutic value of a drug, various methods are used, namely:-

1. The Method of Therapeutic Index of Schwab and Prichard (1951).

A system of "points" is used - a positive for favourable actions of the drug and negative for unfavourable effects. Thus 4 positive points are given if the drug gives very good results when used alone, 2 positive points if only good results are obtained when the drug is used alone and 1 positive point if the drug is good only when used in combination /

combination with other drugs. If toxic effects are present, 4 negative points are recorded, and 2 negative points if therapeutic effects are equivocal. The therapeutic index is expressed by dividing the positive points by the negative points. They studied 12 drugs and by this method assigned indices of 3.1 to benzhexol, 2.8 to caramiphen, 2 to benadryl, 0.8 to stramonium, 0.4 to amphetamine and 0.3 to hyoscine. There is one objection to this method of assessment of drug therapy. Four negative points are awarded when there are toxic effects but this does not take into consideration the severity of the toxic effects. A substance may have only slight therapeutic value but because of minimal toxic effects there will be a small denominator and thus its therapeutic index will be rated excessively high.

2. <u>The Use of Points System</u> (Moore, 1951).

This writer makes a list of ten items to be studied. The items are as follows:-

1. Rigidity
2. Tremor
3. Posture and gait
4. Ease of movement with respect to both gross movements (such as putting on clothes) and fine movements (such as buttoning shirts and vests).
5. Speech.
6. Improvement in morale and alertness.
7. Appetite and weight gain.
8. /

8. Effect on oculogyric crisis and other post-encephalitic phenomena.

9. Effect of substitution of placebos.

10. Subjective feeling of well-being and improvement.

A plus, minus or zero is awarded to each item according to whether the drug produced an improvement, a worsening effect, or no effect on the particular item in question. A score of 8 or over is considered to indicate marked improvement, while a score of 5 - 8 indicates fair improvement and below 5 is supposed to indicate that the patient is virtually unaffected. This method of assessment is not satisfactory as there are considerable variations in the pattern of disability from one patient to another. Thus in a particular patient there may only be four relevant disabilities, but a drug may produce a marked improvement in all of them. On this basis it should therefore be awarded a high score, but on Moore's scale it would be awarded a maximum of 4 points - a rating which would place it among drugs not of proved therapeutic value in Parkinsonism. It is therefore obvious that this method of assessment may fail to do justice to the therapeutic effects of a drug.

It is likely that the most reliable method in arriving at a final evaluation is to combine the results of objective measurements and the response of the patient subjectively. Thus when objective measurements show marked improvement but the patient suffers from disabling side-effects or toxic effects the therapeutic value cannot be considered /

considered to be satisfactory. If the patient's sense of general well-being is greatly improved and yet objective movements (such as muscle power) show marked deterioration, the total result does not support a claim for therapeutic value. It is thus essential to visualise a therapeutic effect in all its dimensions and make an assessment on a broad basis. This usually enables the clinician to grade the result in simple terms, such as Satisfactory, Fair or Poor, and he may well find that the Ward sister and the patient's relatives discover the advantages of a simple classification of this type.

Lastly, it can be said that the results of objective measurement usually run roughly in parallel with an assessment of the patient's condition as determined by the clinician - and especially when the initial degree of disability is moderate. In patients who are only mildly affected it may be difficult to detect any changes by quantitative objective measurements; and in patients with severe disability marked changes in the quantitative objective measurement due to the drug are not often associated with proportional improvement in the patient's general condition. Thus in patients who show fairly normal muscle power while receiving placebo therapy, dynamometer readings do not show any significant increase when the patients are placed on "active" tablets. The effect of drugs on muscle strength is best demonstrated in patients with an appreciable degree of muscle weakness. However in patients who are very weak, doubling of the grip strength is not associated with such striking improvement in general condition.

The /

The reason for this lack of correspondence is that although the values of the grip strength during active drug therapy is double that during placebo therapy, even with optimum medication muscle power may be very considerably less than in a normal person.

It must be emphasised that in the majority of cases the physician's clinical assessment of the patient's condition, e.g., the assessment of excess salivation, the patient's ability to feed himself, dress himself or walk, are in fact objective although they may not be readily measured quantitatively by the use of instruments. Quantitative measurements however, are essential as they add greater accuracy in the assessment of the comparative values of different therapies. It should therefore be used whenever possible. Thus gait can be measured by the time taken to walk a fixed distance; and in order to facilitate detailed scrutiny, cinematographic methods can be used to study the patient's gait and his ability to feed or dress himself.

Out-patient assessment in which the patient is asked to answer set questions are unreliable; and assessments which are based solely on the patient's subjective feelings and impressions are even more misleading. The nature of the answers is affected by many variable factors - intelligence, willingness to co-operate honestly, prejudice acquired from other patients or from reading magazine articles, reluctance to experiment with new preparations, and so on.

This study has shown that "preliminary" assessment of any drugs likely to be of use in the treatment of Parkinsonism can be adequately conducted /

conducted in the manner already described giving each drug for a short period of not more than three weeks. However the final assessment of the clinical usefulness of any drug will depend on the results of a long-term study lasting several months, as such phenomena as the development of tolerance, and the emergence of toxic effect on haemopoietic system, on the liver and on other organs, may not be evident in the course of a short-term study.

The acute experiment lasting four to six hours are of value for rapid screening. It gives information about the effect of the drug on the cardiovascular system, salivation, pupils and muscle power. Measurements of active neck movements are not materially affected and can be omitted. The special value of this form of study is that it can demonstrate the phenomenon of peak activity in the therapeutic effects of a drug. It also reveals the time of onset of drug action and its duration. The most useful items for study are the effects of the drug on salivation and on the power of grip. Patients should be selected, taking into consideration their reliability as witnesses and the degree of physical disability. Patients with very mild degrees of disability are not suitable for study. It is our experience that patients with severe degrees of tremor may not be capable of applying constant pressure by means of the hand; they are not therefore suitable for studying the effect of drugs on gripping power unless the drug also reduces tremor to an appreciable extent. It is advisable to take about 18 hours for the procedure of substituting placebo tablets for active tablets when making a series of controlled observations.

ILLUSTRATIVE CASES

Case 1. R. Pra.

Male, 42 years. History of encephalitis lethargica doubtful. Age 4 years (1922) - tremor of left arm and dysarthria; age 16 years - symptoms disappeared but reappeared when aged 20 years. Gradually deteriorated and was admitted in 1955. Suffers from oculogyric crisis.

On examination in 1960: moderate rigidity, greater on left side. Tremor mainly of upper limbs, worse on left side. Walks fairly well but gait shuffling. Unable to feed himself; excessive salivation ++. Swallows normally. Therapy: benzhexol hydrochloride 15 mg. daily.

RESULTS OF THE TRIAL

Course (i) /on Tablet Z (UK. 738 placebo)/.

Did not feel well. Moaning night and day. Excessive salivation +++. Rigidity increased but gait and deglutition unaffected. Sweating excessively most days. Three oculogyric crises.

Power of grip:

Right hand -	90	72	104	Average 88
Left hand -	28	22	36	Average 28

Active neck movements: 1.4 0.5 2.3 Average 1.4

Writing: Marked apraxia first week (Fig. 47). Unable to write second week. Able to complete task in the third week but took over 15 minutes.

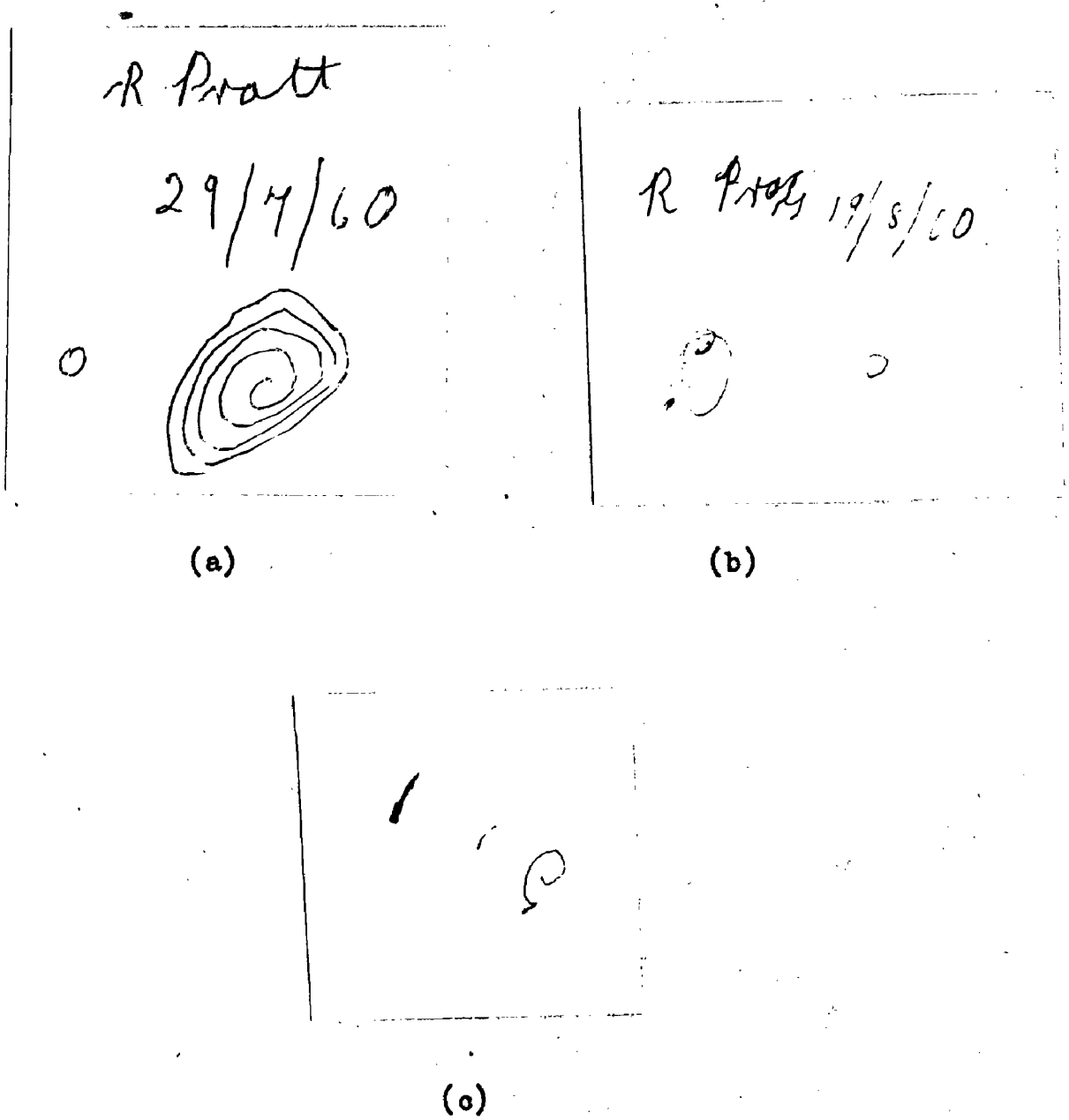
Course (ii) /on Tablet M (Orphenadrine - Disipal)/.

Felt very well. Moaning ceased. Rigidity much less. Excess salivation was greatly reduced. One oculogyric crisis.

Power of grip:

Right hand -	166	170	170	Average 168
Left hand -	46	50	56	Average 51

Active /



(a) (b)

(c)

Fig. 47. Case 1.

Examples of the worst specimens of the handwriting during each period of the drug trial.

(a) During orphenadrine therapy.
(b) During treatment with "UK. 738".
(c) During placebo therapy.

Case 1. R. Pra. (Cont'd).

Active neck movements: 3 3.2 3 Average 3 cm.
Writing: Very good. (Fig. 47).
Side-effects: Involuntary jerking movements of the limbs.

Course (iii) /on Tablet N (UK. 738)/.

Moaning night and day. Excessive salivation ++. Rigidity a little increased. Gait and deglutition unchanged. One oculogyric crisis.

Power of grip:

Right hand -	140	170	120	Average 143
Left hand -	38	40	38	Average 38

Active neck movements: 1.8 2.6 2 Average 2.1 cm.
Writing: Not as good as in the preceding period; more time taken to complete tasks and some degree of apraxia last week (Fig. 47).

Course (iv) /on Tablet Y (Disipal Placebo)/.

Moaning more than in the last period. Incontinent of urine. Rigidity markedly increased. Excessive salivation +++. Severe sweating almost daily. Gait and swallowing unchanged. Two oculogyric crises.

Power of grip:

Right hand -	120	76	120	Average 109
Left hand -	36	26	46	Average 36

Active neck movements: 1.7 1.5 2.5 Average 1.9 cm.
Writing: Apraxia of writing throughout this period (Fig. 47).

COMMENT:

The results of the objective measurements could be correlated with the patients general clinical condition. When he was receiving orphenadrine /

Case 1. R. Pra. (Cont'd).

orphenadrine however he was troubled by involuntary jerky movements of the limbs and because of this rather disagreeable side-effect, orphenadrine was regarded as giving a "fair" result in this patient. Both UK. 738 and the placebos were classed as giving "poor" results.

Case 2. A. Bis.

Woman, 54 years. Admitted 1932. Para 5^{+2}. 1923 "nervous breakdown" with alteration of sleep rhythm and excessive salivation. Oculogyric crisis (mild) began in 1943. Deteriorated, and by 1949 bedridden.

1960. Rigidity very marked, especially lower limbs; left side worse than right. Able to feed self. Swallowing easily. Practically no tremor. Receiving benzhexol 30 mg. daily.

RESULTS OF TRIAL

Course (i) /on Tablet V (Orphenadrine placebo)/.

Unable to feed herself: hand stops halfway to mouth and remains there almost indefinitely. Swallowing fairly well. Excessive salivation ++. No oculogyric crises.

Power of grip:

Right hand -	64	90	94	Average 82
Left hand -	44	52	54	Average 50
Active neck movements:	1.8	2.4	2.4	Average 2.2 cm.

Course (ii) /on Tablet P (Orphenadrine)/.

Feeding herself without help; turning about more freely in bed and able to get sweets out of her locker. Excess salivation ± . Swallowing well. Patient bright and cheerful. No oculogyric crises.

Case 2. A. Bis. (Cont'd.)

Power of grip:

Right hand -	116	94	74	Average 94
Left hand -	64	80	56	Average 64
Active neck movements:	4	3.9	2.6	Average 3.5 cm.

Course (iii) /on Tablet S (UK. 738 placebo)/.

Unable to feed herself, especially last two weeks. Swallowing fair. Excess salivation ++. Three oculogyric crises.

Power of grip:

Right hand -	102	104	96	Average 101
Left hand -	68	76	60	Average 68
Active neck movements:	3	2.5	2.3	Average 2.6 cm.

Course (iv) /on Tablet R (UK. 738)/

Better than in the last period of treatment. Excessive salivation +. Swallowing well last two weeks. Unable to feed herself: able to get food into the mouth but jaw movement arrested while masticating the food. Three oculogyric crises.

Power of grip:

Right hand -	92	76	100	Average 88
Left hand -	68	50	60	Average 59
Active neck movements:	2.6	2.5	2.8	Average 2.6 cm.

COMMENT:

There was no significant difference between the quantitative objective measurements in all four periods. The patient improved most when receiving orphenadrine - as judged by ability to feed without assistance, reduction of salivation, changes of mood, etc.

The /

Case 2. A. Bis. (Cont'd.)

The results of the clinical trial aiming at determining the relative merits of Orphenadrine, "UK. 738" and a placebo in this patient can be summed up thus:-

Orphenadrine - satisfactory; "UK.738" - fair; placebo - poor.

Case 3. H. Lan.

Woman, aged 54 years. 1925 - encephalitis lethargica lasting six months. Soon after, involuntary tremor left side and excessive salivation. 1959 stated to have had oculogyric crisis but no definite deviation of the eyes observed since admission in 1960.

Findings on admission:-

Moderate rigidity - mainly left side. Tremor mild left-sided. Gait slow and some retropulsion. No excess salivation. Able to feed and dress herself. Swallowing well.

RESULTS OF THE TRIAL

Course (i) /on Tablet N ("UK. 738")/.

Weepy and depressed. Often incontinent of urine. Unable to dress herself but able to feed herself, and swallowing well. Gait - fairly good.

Power of grip:

Right hand -	240	212	240	Average 230
Left hand -	24	30	32	Average 28

Active neck movements: 4.2 4 5 Average 4.4 cm.

Writing: Good.

Course /

Case 3. H. Lan. (Cont'd.)

Course (ii) /on Tablet Y (Orphenadrine placebo)/.

Condition worse than in the last phase of treatment. Now unable to feed herself without help; gait unsteady with retropulsion ++. Great difficulty in getting up from a chair (Fig. 48). Rigidity markedly increased; and she complained of stiffness. Excess salivation ±. Involuntary flexor spasms of the left hand with increase in the deformity.

Power of grip:

Right hand -	240	220	240	Average 233
Left hand -	28	40	46	Average 38
Active neck movements:	1.5	2	6	Average 3.2 cm.

Writing: Normal.

Course (iii) /on Tablet Z (UK. 738 placebo)/.

Condition still the same although on a few days she was able to dress and feed herself.

Power of grip:

Right hand -	240	240	240	Average 240
Left hand -	38	50	30	Average 39
Active neck movements:	5.5	2	2.5	Average 3.3 cm.

Writing: No change.

Course (iv) /on Tablet M (Orphenadrine)/.

Dramatic change. Very well and cheerful. Gait: good and no retropulsion (Fig. 39, page 216). Able to rise from a chair without difficulty (Fig. 48). Rigidity much less; no further flexor spasms. Incontinence of urine ceased. Able to dress and feed herself. Salivation ceased to be excessive.

Power /

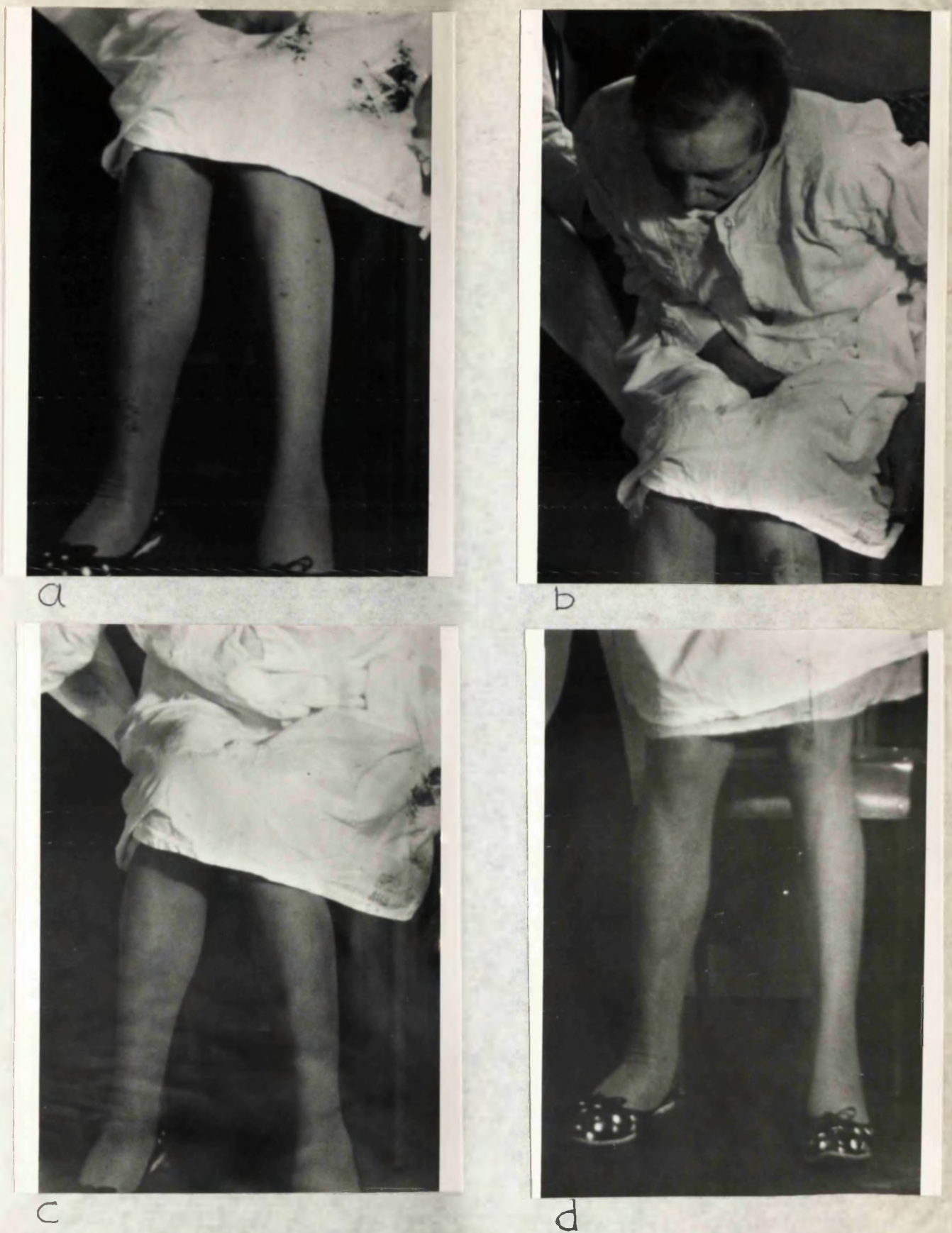


Fig. 48. Case 3. "Stills" from cinematographic study of the patient's attempt at getting up from a chair during treatment with placebo tablets. (a) Start. (b) After 14 sec. (c) After 28 sec. (d) After 42 sec.

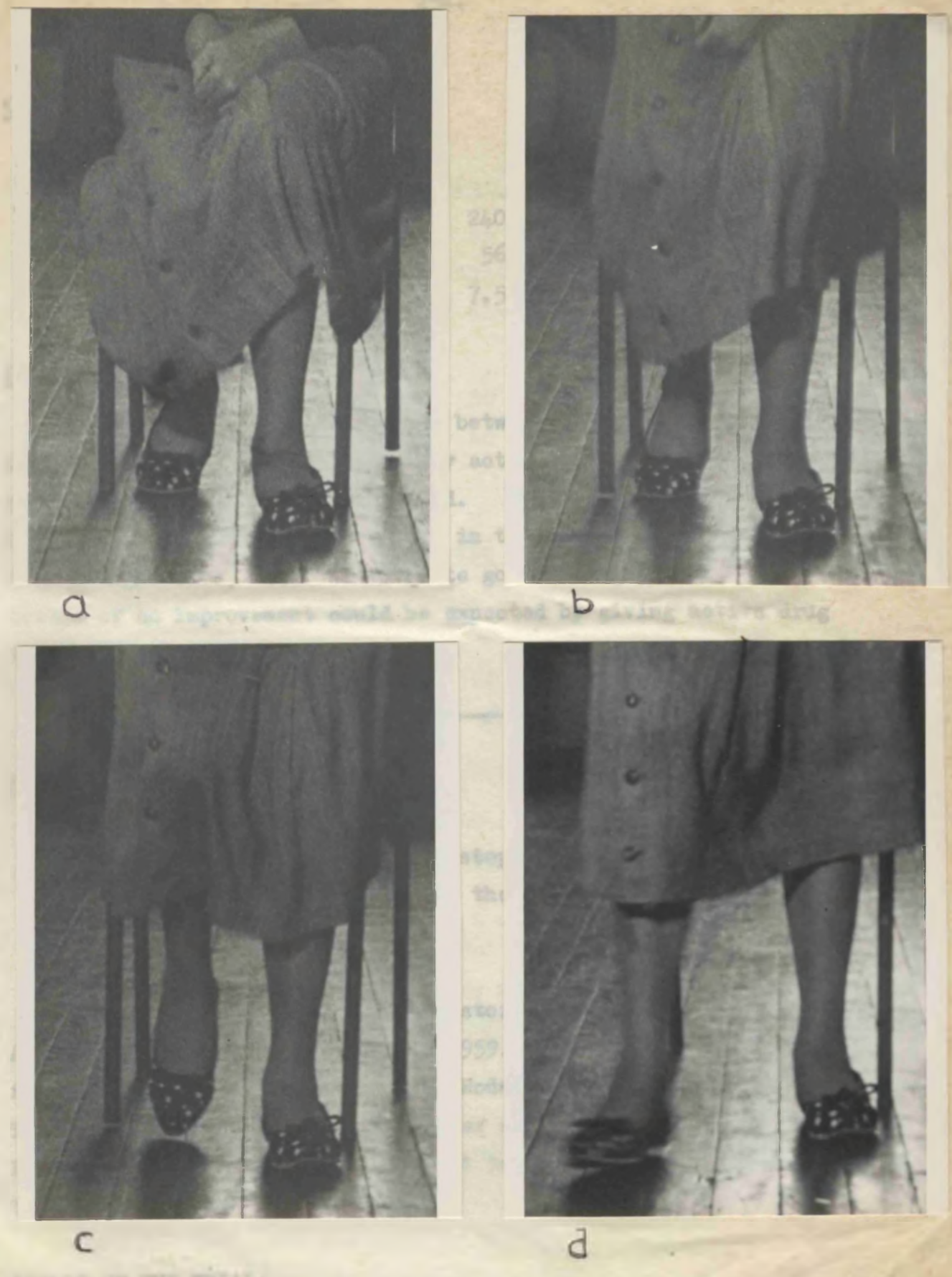


Fig. 49. Case 3. "Stills" from cinematographic study of the patient's attempt to rise from a chair during treatment with orphenadrine 100 mg. t.i.d. (a) Start. (b) After 0.3 sec. (c) After 0.72 sec. (d) After 1 sec.

Case 3. H. Lan. (Cont'd).

Power of grip:				
Right hand -	240	240	240	Average 240
Left hand -	58	56	46	Average 53
Active neck movements:	7.3	7.5	5.8	Average 6.8 cm.

COMMENT:

There was a close correlation between the clinical condition and some objective measurements, namely active neck movements, and the power of grip of the weak left hand. There were no significant differences in the handwriting and in the power of grip of the very strong right hand; these were quite good during placebo therapy and little or no improvement could be expected by giving active drug therapy.

Case 4. J. McM.

* indicates that the drug was stopped prematurely, that is before the patient had taken the drug for 21 days according to the schedule.

Male, aged 50 years. 1924 history of encephalitis lethargica. Admitted 1933. Clinical review, 1959. Patient bedridden with flexion deformity of both knees. Moderate degree of rigidity. Tremor all limbs. Poor muscle power and unable to feed himself. Difficulty in swallowing. Frequent severe sweating crises. Receiving 15 mg. benzhexol daily.

RESULT OF THE TRIAL:

Course /

Case 4. J. McM.(Cont'd.)

Course (i) /on Tablet P (Orphenadrine)/.

Patient had slight improvement on his condition during benzhexol therapy. Excess salivation was a little less and his power of deglutition was regarded as fair. Six sweating crises.

Power of grip:

Right hand -	50	38	46	Average 45
Left hand -	38	40	34	Average 37

Writing: See Fig. 50.

Course (ii) /on Tablet V (Orphenadrine placebo)/.

No change in patient's condition. Three sweating crises.

Power of grip:

Right hand -	18	18	10	Average 15
Left hand -	26	ø	24	Average 25

ø Unwilling to have the power of grip tested.

Writing: Was unwilling to write except in the first week (a few days after starting this course).

Course (iii) /on Tablet R (UK. 738)/.

There were two important changes in his condition. He was swallowing much better (graded F. Good). Secondly he had no sweating crises.

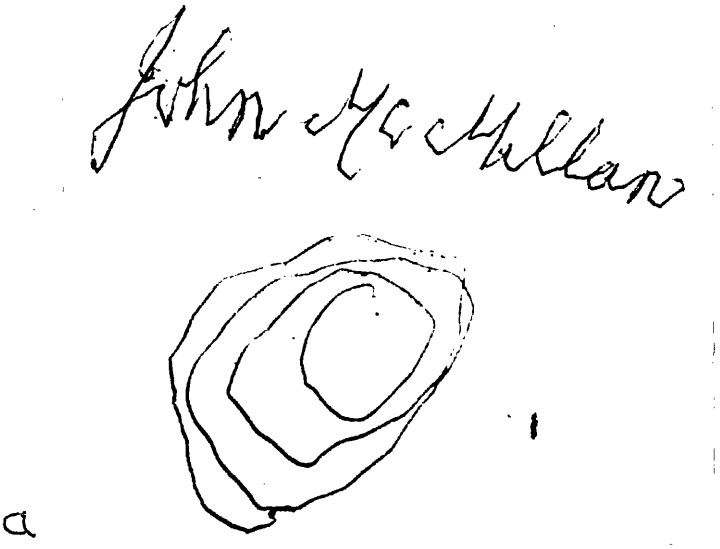
Power of grip:

Right hand -	30	28	40	Average 33
Left hand -	32	32	38	Average 34

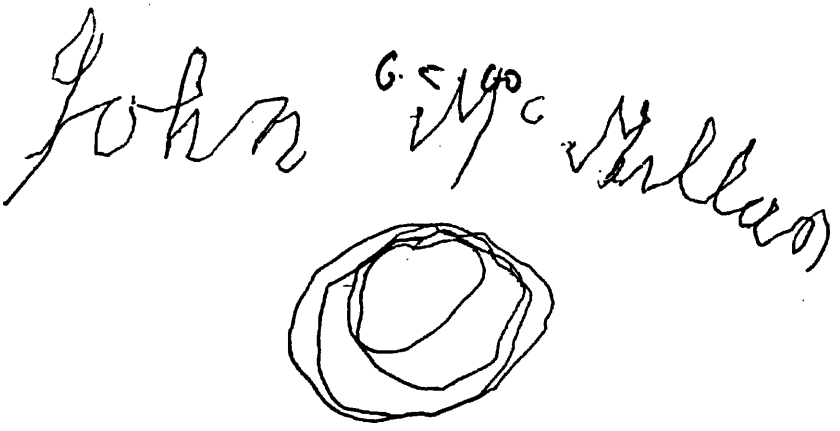
Writing: See Fig. 50.

Course (iv) /on Tablet S (UK. 738 placebo)/.

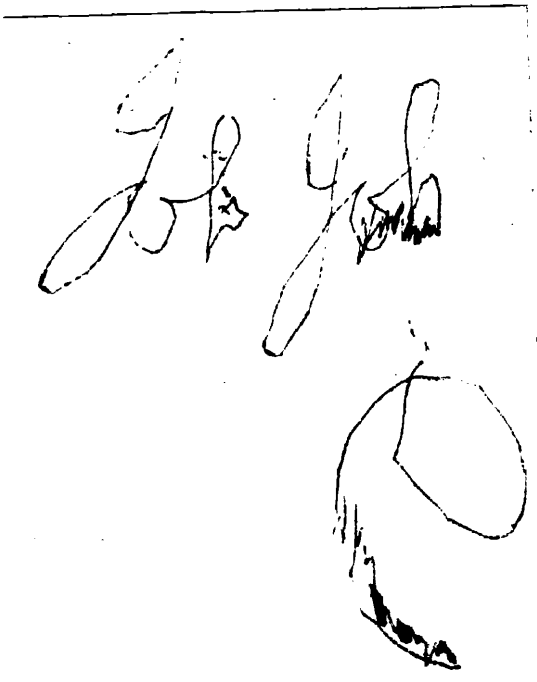
His /



a



b



c

Fig. 50.
Patients handwriting while on various kinds of drug therapy.

(a) Orphenadrine 100 mg. t.d.s.

(b) "UK. 738", 4 mg. t.d.s.

(c) Placebo, 2 tablets t.d.s.

Case 4. J. McM. (Cont'd.)

His swallowing was worse (graded as poor - fair). Three sweating crises.

Power of grip:

Right hand -	12	8	4	Average 8
Left hand -	26	26	14	Average 22

Writing: Unwilling to write on two of three occasions and on the one occasion when he was agreeable to the writing, showed marked degree of akinesia (see Fig. 50).

COMMENT:

Although the results of quantitative objective measurements including handwriting were best when the patient was receiving orphenadrine (Disipal), the general condition (as assessed by salivation, ability to swallow, sweating crises) during this period was no better than during placebo therapy. In fact he had more sweating crises during orphenadrine therapy than during placebo therapy. UK. 738 on the other hand abolished the sweating crises and markedly relieved his difficulty in swallowing. In the final assessment of the merits of the individual drugs used for this patient, orphenadrine was classed with placebo therapy as giving poor results while the result of treatment with UK. 738 was classed as fair. This case illustrates the fact that it is undesirable to rely solely on quantitative objective methods of assessment without taking into consideration the patient's general clinical condition.

N.B. Neck movements were not measured as it was not possible to position him in such a way as to obtain standard conditions every time.

Case 5. A. McL.

Woman aged 61 years. Admitted 1949. 1919 attack of influenza during which her back was paralysed. Recovered and worked as a seamstress until 1937, when she was unable to continue because of tremor. Just before admission was unable to manage household duties.

Clinical review, 1960. Tremor ++, arms, legs and mouth. Severe scoliotic deformity but able to walk about. Reflexes normal. Receiving benzhexol 30 mg. daily.

RESULTS OF THE TRIAL:

* Course (i) /on Tablet Y (Orphenadrine placebo)/.

Did not feel well at all. Tremor worse. Unable to rise from a chair, feed herself or dress herself. Gait very slow. Sweating +. Palpitations ++ especially at night. Swallowing and appetite good.

Power of grip:

Right hand - 60

Left hand - 72

Active neck movements: 5.2 cm.

Writing - Unable to write.

Course (ii) /on Tablet "UK. 738"/.

Felt much better during first two weeks but her condition worsened somewhat in the third week. Able to get up from a chair without difficulty. Able to feed self and dress self. Sweating ±. Tremor was still severe.

Power of grip:

Right hand -	90	100	108	Average 99
Left hand -	90	104	96	Average 97
Active neck movements:	6.2	6.5	6.5	Average 6.4 cm.

Writing /

Case 5. A. McL. (Cont'd.)

Writing: Unable to write.

Course (iii) /on Tablet M (Orphenadrine)/.

Further improvement. Tremor although showed some improvement, was still bad.

Power of grip:

Right hand -	110	120	120	Average 116
Left hand -	102	104	110	Average 108

Active neck movements: 6.5 6.5 6.5 Average 6.5 cm.

Writing: Unable to write.

* Course (iv) /on Tablet Z (UK. 738 placebo)/.

Deteriorated. Patient unable to walk, feed or dress herself. Increased tremor. She complained of palpitations and was sweating excessively. She was incontinent of urine during the later part of this period.

Power of grip:

Right hand -	60	70	Average 65
Left hand -	60	76	Average 68

Active neck movements: 6.5 5.0 Average 5.6 cm.

Writing: Unable to write.

COMMENT:

There was a close relationship between the results of the objective measurements and the patient's clinical state. She was unable to write because of emotional exaggeration of tremor when instructed to write her name, etc.

Case 6. J. Pat.

Woman, 57 years.

Following tonsillectomy operation in Australia in 1928 developed muscular weakness on one side of the body and tremor on the other. First oculogyric crisis 1942: admitted 1946.

Clinical review, 1960. Moderate degree of rigidity all limbs; more marked in left arm. Festinant gait; unable to feed herself but deglutition unaffected. Excess salivation ++; had to use a bib continuously. Tremor ++; had received Tincture of Stramonium 2 ml. per day.

RESULT OF THE TRIAL:

Course (i) /on Tablet Z (UK. 738 Placebo)/.

Condition unchanged.

Power of grip:

Right hand -	56	64	80	Average 66
Left hand -	26	32	72	Average 43

Active neck movements: 1.5 4.8 3.7 Average 3 cm.

Writing: (Fig. 41, page 223).

Course (ii) /on Tablet M (Orphenadrine)/.

Excess salivation ± : bib no longer needed. Tremor +. Able to feed herself (except tea and soup). Gait less festinant. Now able to lace her shoes.

Side-effect: Complained of dizziness 1-1½ hours after taking the tablets, and lasting 1-2 hours.

Two oculogyric crises.

Power of grip:

Right hand -	120	116	112	Average 116
Left hand -	90	90	96	Average 92

Active neck movements: 5.5 4.8 5 Average 5.1 cm.

Writing /

Case 6. J. Pat. (Cont'd.)

Writing: (Fig. 41, page 223).

Course (iii) /on Tablet N (UK. 738)7.

General condition worse. Excess salivation ++ : using bib again. Tremor ++. Unable to feed herself. Five oculogyric crises.

Power of grip:

Right hand -	116	122	126	Average 121
Left hand -	90	70	90	Average 83
Active neck movements:	4.2	4.7	4	Average 4.3 cm.

Writing: (Fig. 41, page 223).

Course (iv) /on Tablet Y (Orphenadrine Placebo)7.

Further deterioration. Now unable to walk without support. Voice very faint. Seven oculogyric crises.

Power of grip:

Right hand -	96	90	82	Average 96
Left hand -	36	70	44	Average 50
Active neck movements:	2	2.5	3	Average 2.5 cm.

Writing: (Fig. 41, page 223).

COMMENT:

In this patient there is also a close correlation between the objective measurements and the patient's clinical condition with regard to orphenadrine and the placebos. However UK. 738 appeared to have about the same effect on muscle strength and range of active neck movements as orphenadrine but the patient's clinical state was much worse than during orphenadrine therapy. In the final assessment of the values of these drugs in this patient, the classification was as follows:

(i) /

Case 6. J. Pat. (Cont'd.)

(i) Orphenadrine (Disipal) - satisfactory.
(ii) UK. 738 - poor.
(iii) Placebos - poor.

Case 7. T. Wyp.

Male, 56 years. Admitted 1955. 1928 history suggestive of encephalitis lethargica. Oculogyric crisis while at home but none since admission.

Clinical review, 1959. Patient independent. Very little rigidity. Tremor all limbs, lips and tongue of moderate severity. Some difficulty in swallowing. Gait and muscle power good. Reflexes normal. Receiving benzhexol 10 mg. t.i.d.

RESULTS OF THE TRIAL:

Course (i) /on Tablet R (UK. 738)/

Patient was very well throughout this period. Swallowing well during this period.

Power of grip:

Right hand -	240	240	240	Average 240
Left hand -	240	222	240	Average 234
Active neck movements:	5.5	5.0	7.3	Average 5.8 cm.

Writing: Good.

*Course (ii) /on Tablet S (UK. 738 placebo)/, 6 days.

Suffered from nausea and vomiting, especially on the second and third days of this period. Did not want to be out of bed. Tremor increased /

Case 7. T. Wyp. (Cont'd.)

increased ++. He complained of tendency to stare into space for long periods. Swallowing - poor or fair. No real increase in rigidity.

Power of grip:

Right hand - 240

Left hand - 220

Active neck movements: 5.8 cm.

Writing: Good in spite of great increase in tremor.

Course (iii) /on Tablet P (Orphenadrine)7.

Dramatic improvement. Felt very well. Tremor now +. Swallowing well.

Power of grip:

Right hand -	240	240	240	Average 240
Left hand -	240	210	240	Average 223

Active neck movements: 6.8 6.5 7.0 Average 6.4 cm.

Writing: Good.

*Course (iv) /on Tablet V (Orphenadrine Placebo)7, 3 days.

Nausea and vomiting ++. Tremor increased ++. Patient not willing to get up.

Power of grip:

Right hand - 240

Left hand - 205

Active neck movements: 5.5 cm.

COMMENT:

Results of the clinical trial in this case were classified solely according to the patient's clinical condition in each phase of the investigation. The differences in the objective measurements were not significant. /

Case 7. T. Wyp. (Cont'd).

significant. This is probably due to the fact that even when he was receiving placebo tablets his grip strength, range of active neck movements and handwriting were good.

Case 8. R. Cai.

Woman, aged 64 years. Admitted 1951. Encephalitis lethargica 1924. Illness lasted six months. Oculogyric crisis two years later. Receiving benzhexol 5 mg. t.i.d.

Clinical review, 1960. Flexion contractures all limbs, especially on the left side. Mild generalised tremor. Severe degree of rigidity - worse on left side. Tendon jerks not elicitable except the right biceps jerk. Plantar responses were flexor. Suffers from moderate degree of excess salivation and has great difficulty in feeding herself. Swallows well.

RESULTS OF THE TRIAL:

Course (i) /on Tablet S (UK. 738 Placebo)/.

Unable to feed herself. She was dull and depressed, especially in the first week. Great difficulty in swallowing. Two oculogyric crises.

Power of grip:

Right hand	-	18	22	30	Average 23
Active neck movements:		1.7	2	2	Average 1.9 cm.

Writing: Good.

Course (ii) /on Tablet R (UK. 738)/.

More /

Case 8. R. Cai. (Cont'd.)

More cheerful. Was able to feed herself completely in the last 7 days. Swallowing improved; regarded as good in the last week. No change in salivation.

Power of grip:

Right hand - 50 30 56 Average 45

Active neck movements: 2.6 1.8 2.2 Average 2.2 cm.

Course (iii) /on Tablet P (Orphenadrine)/.

Very cheerful. Fed herself completely. Swallowing good. No change in salivation.

Power of grip:

Right hand - 52 72 68 Average 64

Active neck movements: 2 3 2.8 Average 2.6 cm.

*Course (iv) /on Tablet V (Orphenadrine Placebo)/ 4 days.

Depressed and dull. Appetite very poor. Nausea and vomiting. +. Unable to feed herself. No change in salivation. Rigidity much increased.

Power of grip:

Right hand - 32

Active neck movements: 2 cm.

Writing: Unable to write because she could not hold the pen.

COMMENT:

There was close correlation between the results of objective measurements and the patient's clinical condition.

Case 9. J. Cam.

Male, aged 57 years. 1917 encephalitis lethargica. Admitted 1943. Clinical review 1959. Moderate rigidity. Tremor all limbs, tongue and jaw. Unable to feed himself. Able to dress self with occasional help. Excess salivation +. Gait:- he walked slowly but fairly well. No difficulty in swallowing. Suffered from severe sweating crisis. Receiving benzhexol 10 mg. thrice daily.

RESULTS OF THE TRIAL:

*Course (i) /on Tablet N (UK. 738)/ 5 days.

Gait worse - falling ++. Unable to dress himself. A little drowsy; unwilling to leave his bed. Severe sweating crisis every night. No change in degree of excess salivation, rigidity or tremor.

Power of grip:

Right hand - 52

Left hand - 20

Active neck movements: 2.3 cm.

*Course (ii) /on Tablet Y (Orphenadrine placebo)/, 3 days.

Much worse. Very drowsy. In bed most of the time. Rigidity markedly increased. On the third day he lapsed into catatonic stupor. Was incontinent of urine. He was withdrawn from the double blind trial and was then given "UK. 738" 2 mg. intramuscularly. This was effective in 40 minutes and he was roused from his stupor. (See Table 23 for details of his general clinical condition.) Figure 51a shows the patient in catatonic stupor.

He was then placed on Tab. UK. 738 4 mg. t.i.d. but two days later he relapsed into catatonic stupor and was roused about 20 minutes after receiving 2 mg. UK. 738 intravenously. Figure 51b shows the same patient two hours after receiving this treatment. The daily dosage of his oral UK. 738 was now increased to 20 mg. daily - 4 mg. five /

Case 9. J. Cam. (Cont'd.)

five times daily. His general condition was much better and after four days it was considered safe and perhaps advisable to reduce the dose of his "UK. 738" to the standard daily dose of 12 mg. daily (4 mg. t.d.s.). He deteriorated somewhat as he was a little drowsy and was only able to walk for a few yards. His sweating crises were frequent and severe. The "UK. 738" was discontinued after three weeks and he was placed on orphenadrine 100 mg. thrice daily. He was generally brighter but continued to sweat daily. He however complained of some difficulty in starting the act of micturition but he had no retention of urine. After one month benzhexol 10 mg. t.i.d. was substituted for orphenadrine. Within 48 hours he showed marked improvement in his overall condition.

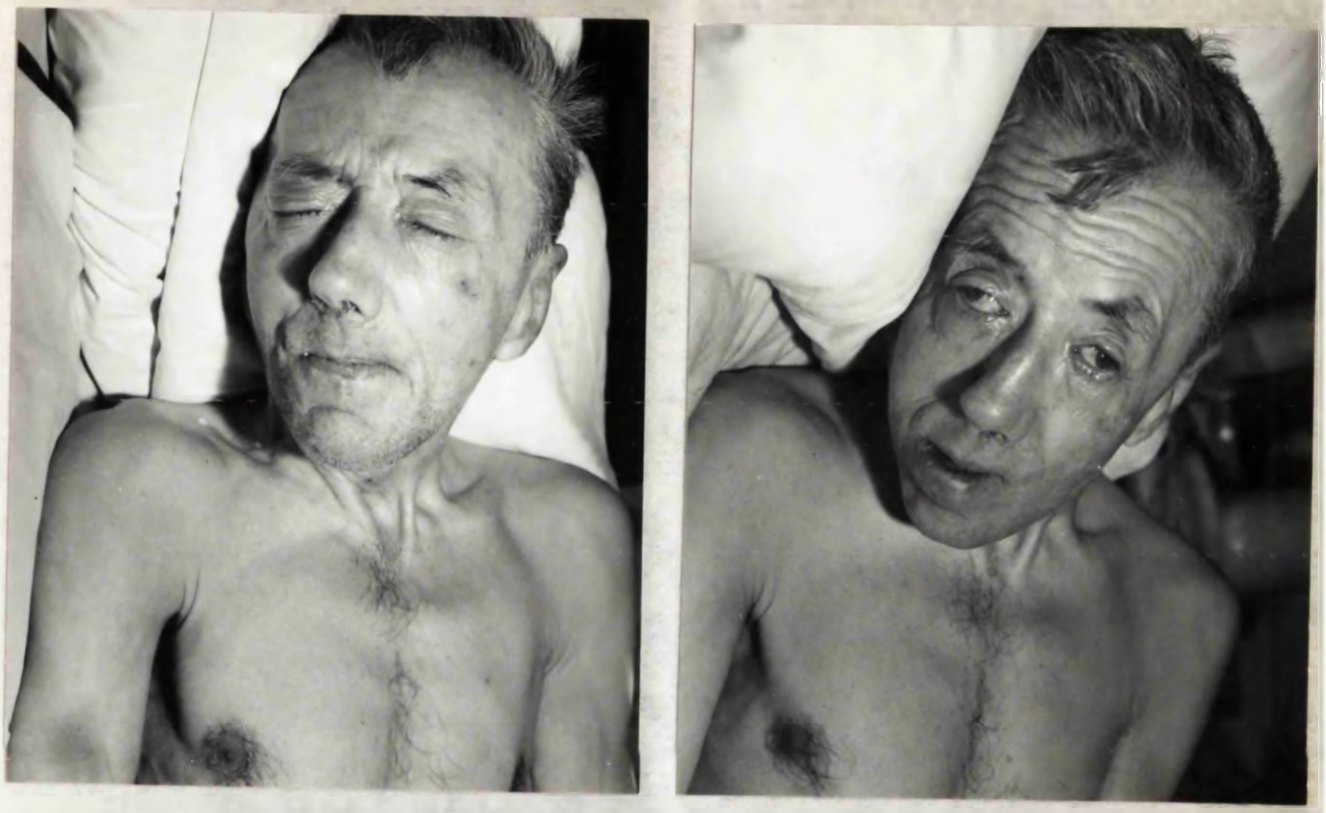
COMMENT:

The first point of interest is the fact that 2 mg. of "UK. 738" given intravenously or intramuscularly was effective in rousing a patient from catatonic stupor into a state of full consciousness in 20 to 40 minutes. The intensely rigid state was also appreciably reduced. This suggests that the drug might be useful in the treatment of catatonic stupor of schizophrenia, a condition not unlike that seen in Parkinsonism. The other important point is that in the individual patient it may be possible to obtain a greater therapeutic effect by increasing the maximum daily dosage of "UK. 738" from the standard 12 mg. daily to about 20 mg. daily without any unwanted side-effects developing.

Finally, in this patient benzhexol was probably the drug of choice although at a dose level of 30 mg. daily he still had an appreciable degree of residual Parkinsonism.

TABLE 23: Case 9. In Catatonic Stupor. "UK. 738" : 2 mg. given I.M. at 4.12 p.m.

Time	Grip Right	Grip Left	Rigidity	Biceps Jerk	State of consciousness	Tremor	Elbow Jt. passive movement	Heart Rate/min.
4.10 p.m.	Unable to squeeze the sphygmomanometer bag.		R. 4 L. 4	+ +	Very unresponsive even to painful stimuli.	Only of mouth ++.	R. 146° L. 120°	84
4.22 p.m. (10 min.)			same	same	same	same	same	84
4.32 p.m. (20 min.)			R. 3 L. 3	same	Beginning to feel the pain of extension of elbow joint.	same	R. 155° L. 140°	84
4.42 p.m. (30 min.)			R. 3 L. 3	same	More responsive. Tried to mumble something.	R.hand now also starting to shake.	R. 155° L. 140°	84
4.52 p.m. (40 min.)			R. 3 L. 3	same	Still more responsive. Can now open eyes for a brief moment and answers questions.	Both hands now show some degree of tremor.	R. 165° L. 155°	84
5. 2 p.m. (50 min.)			R. 2+ L. 2+	same	Still more responsive. Can now speak more intelligently.	same	R. 170° L. 158°	84
5.12 p.m. (1 hour)			R. 2+ L. 2+	same	Asked for water to drink. Can keep eyes open for longer period.	same	R. 172° L. 168°	82
5.22 p.m. (70 min.)			R. 2+ L. 2+	same	As in the preceding period.	same	R. 172° L. 167°	84



(a) (b)

Fig. 51. Case 9. Patient aged 57 years suffering from post-encephalitic Parkinsonism.

(a) In catatonic stupor three days after receiving placebo tablets.

(b) The same patient two hours after receiving 2 mg. of "UK. 738" intravenously. (See Text).

SUMMARY.

The relative therapeutic value of orphenadrine and "UK. 738" (Sandoz) were studied by means of a double blind trial. Orphenadrine 100 mg. thrice daily was found to be about three times as effective as "UK. 738" 4 mg. t.d.s.

The methods of assessment of the efficacy of drug therapy in Parkinsonism are reviewed and the value of objective measurements is demonstrated. It can be said that the results of objective measurements usually run roughly in parallel with an assessment of the patient's condition as determined by the clinician - and especially when the initial degree of disability is moderate.

By means of "acute" experiments it was shown that after oral administration of orphenadrine, peak activity occurred in about two hours whereas peak activity due to benzhexol occurred in two to three hours. It was not possible to demonstrate clearly defined peak activity for the drug "UK. 738". Failure to carry out the objective tests at the time of maximal activity of drugs is an important source of fallacy in clinical trials designed to assess the relative merits of preparations used to combat the disabilities associated with Parkinsonism.

CHAPTER VII.

THE SITES AND MODE OF ACTION OF ORPHENADRINE AND OTHER DRUGS USED FOR THE RELIEF OF RIGIDITY AND MUSCLE WEAKNESS IN PARKINSONISM

INTRODUCTION

This investigation was begun after eighteen months of wholetime clinical study of the manifestations of Parkinsonism. The work also included observations on the response of the various physical disabilities to drug therapy, using orphenadrine, N-ethyl-nortropine benzhydryl ether hydrobromide ("UK. 738") and benzhexol (see Chapter VI).

From clinical experience it became very clear that the skeletal musculature is involved to an important extent in the rigidity and weakness of Parkinsonism. The patients tire easily; and the deformities are mainly due to weakness and rigidity of the skeletal musculature. It seemed therefore that there was ample justification for concentrating primarily on a study of the pharmacological effects on skeletal muscle of drugs used in the treatment of Parkinsonism as seen clinically.

Most of this study has been devoted to the pharmacological actions of orphenadrine because this has been found to be one of the most effective /

effective drugs in clinical use today for the relief of Parkinsonism. For a pharmacological study it has the advantage that it is readily soluble in water, whereas benzhexol and especially "UK. 738" are much less soluble. The manufacturers of UK. 738 recommend dissolving it in chloroform or ethanol but this procedure would necessitate carrying out control experiments using the solvents alone. Hence UK. 738 and benzhexol were mainly used in experiments where very dilute solutions were needed and where it was therefore practicable to use weak aqueous solutions. In the later part of this study ethopropazine became available and it was used in later experiments as it was more readily soluble in water than benzhexol or UK. 738.

After discussing the clinical problem with experimental pharmacologists, it was decided that the first part of the study should consist of experiments to investigate whether orphenadrine prevented muscle spasms (contractures) induced by suxamethonium in the hen. It was considered that the contracture of the skeletal muscle in the hen had something in common with the rigidity of Parkinsonism ("spasm of muscles"). It was further decided to study the effect of orphenadrine on the response to indirect tetanisation of skeletal muscle and also the effect on post-tetanic fatigue. The results of this study were of some interest and the experiments were repeated upon a mammal (the cat). Because of the effect not yet described, of orphenadrine on neuromuscular block induced by suxamethonium, the effect of this drug on neuromuscular block caused by tubocurarine was also studied. The

results /

results of these observations led to experiments to find out if orphenadrine itself had any neuromuscular blocking activity and whether certain monosynaptic and polysynaptic spinal reflexes were affected. Finally, in view of a possible stimulant or depressant effect on the spinal cord, the effects of orphenadrine on the cerebral cortex were examined by investigating its influence on the convulsant activity of leptazol.

The method of approach in this study is somewhat different from that adopted by Bijlsma and his colleagues (Bijlsma et al. 1956). Their paper on the pharmacology of orphenadrine is the most comprehensive study which has so far appeared, but the effect of this drug on skeletal muscle was not studied.

When considering the pharmacology of drugs used in the treatment of Parkinsonism the question arises: Do they all produce their effect by one hypothetical mode of action - for example, by a central anticholinergic effect on the midbrain, diencephalon and basal ganglia? On the supposition that this is true, several workers have tried to find out if a particular screening test (carried out on laboratory animals) could be devised which would indicate whether a drug is likely to be of use in the treatment of Parkinsonism in man.

The screening tests, each of which has its advocates, are:-

1. Depression of the flexor reflexes in the thalamic cat (De Maar, 1956; Bijlsma et al. 1956).
2. Depression of the activation of the E.E.G. produced by /

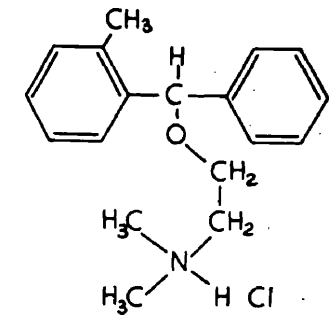
by the stimulation of the brain stem reticular formation in experimental animals (Rinaldi and Himwich, 1955).

3. Inhibition of the tremor induced by Tremorine (1,4-dipyrolidino-2-butyne) (Everett, Blockus and Sheppard, 1956; Blockus and Everett, 1957) or by nicotine (Bovet and Longo, 1951).

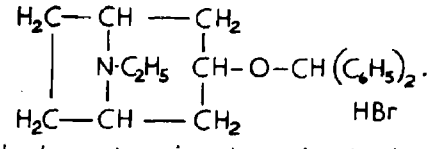
The work to be reported in this chapter was therefore carried out to find out if alternative mechanisms could be found to explain the effectiveness of orphenadrine in Parkinsonism.

Orphenadrine is closely related chemically to diphenhydramine (Benadryl) and differs from it by the possession of an orthomethyl substituent on one of the benzene rings. This slight modification of the molecule of diphenhydramine has reduced its antihistaminic activity but increased its atropine-like action.

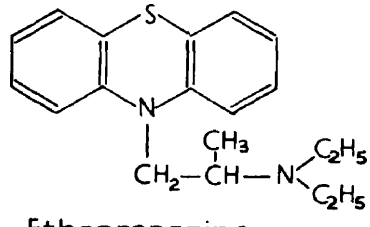
N-ethyl-nortropine benzhydryl ether hydrobromide (UK. 738) is a synthetic tropine derivative and chemically related to atropine. Figs. 52, 53, and 54 show the chemical structure of orphenadrine, UK. 738, and other chemical substances used in this study.



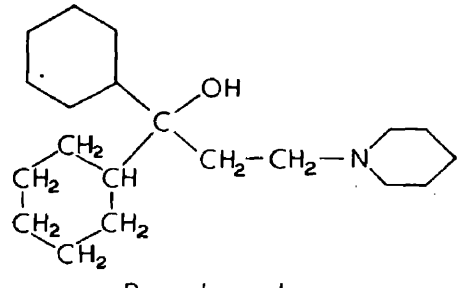
Orphenadrine



N-ethyl-nortropine benzhydryl ether hydrobromide (UK 738)



Ethopropazine



Benzhexol

Fig. 52. The structural formulae of orphenadrine, N-ethyl-nortropine benzhydryl ether hydrobromide (UK. 738), Ethopropazine and benzhexol.

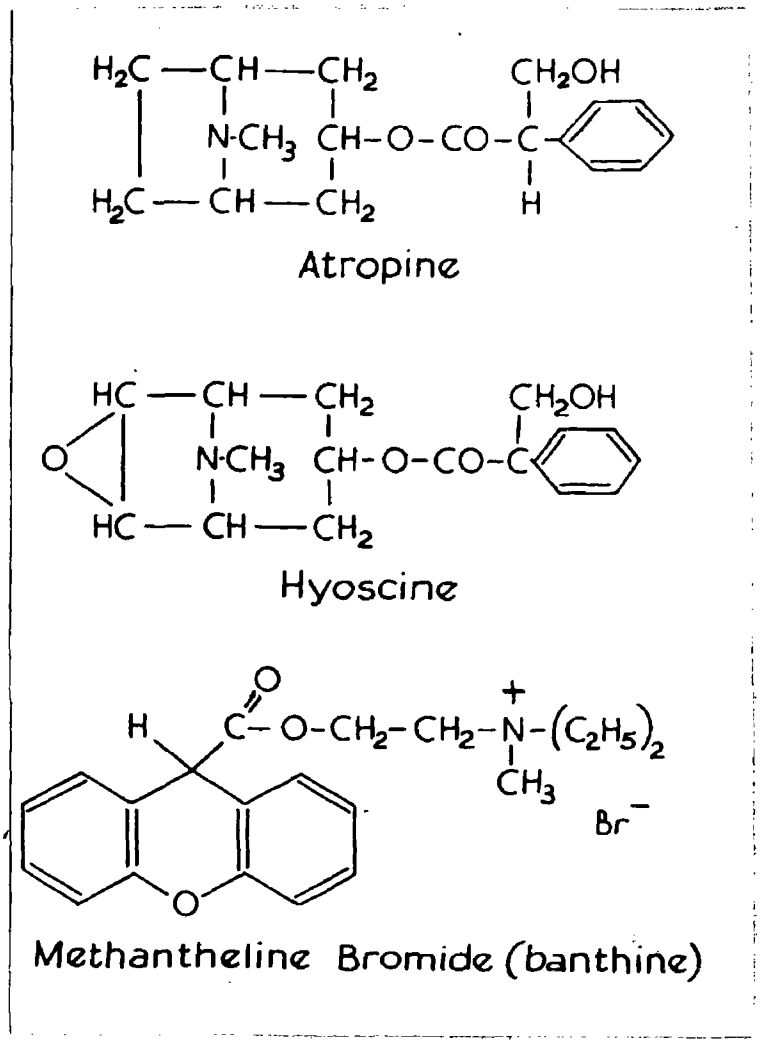
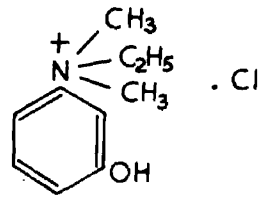
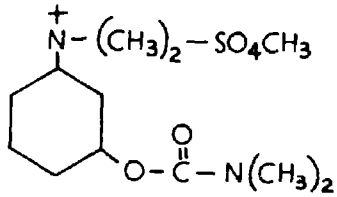


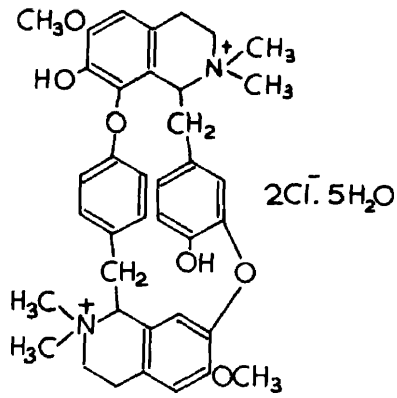
Fig. 53. The structural formulae of atropine, hyoscine, and methantheline bromide.



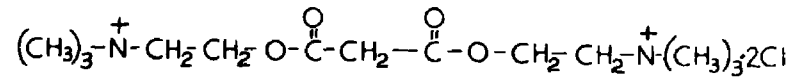
Edrophonium Chloride (Tensilon)



Prostigmine Methyl sulphate



Tubocurarine Chloride



Suxamethonium Chloride

Fig. 54. The structural formulae of edrophonium chloride (Tensilon), prostigmin methyl sulphate, tubocurarine chloride, and suxamethonium chloride.

EXPERIMENTAL

1. Hen Gastrocnemius Muscle - Sciatic Nerve Preparation

METHOD

Hens weighing between 1.5 and 2.0 kg. were used. The hen was laid on its side and the feathers in front of the forearm of the outstretched wing were pulled out to expose the forearm vein. Anaesthesia was induced with a solution of sodium pentobarbitone given slowly intravenously in a dose of 40 to 50 mg. per kg.

The anaesthetised hen was laid on its back upon the operating table and the trachea was cannulated in the manner described on page 292 and connected to a Starling type of artificial respirator. The external jugular vein was then cannulated and connected to a 50 ml. burette. In some of the experiments one of the common carotid arteries was also cannulated and connected to a mercury manometer for blood pressure recording.

The left leg was prepared for indirect stimulation of the gastrocnemius muscle *via* the sciatic nerve. The leg was held with its long axis perpendicular to the operating table and fixed rigidly by means of two clamps, one at the knee joint and the other just beyond the insertion of the Achilles tendon. The gastrocnemius muscle was partially dissected free from the surrounding tissues and the Achilles tendon severed near its insertion into the calcaneus. A strong linen thread /

thread was tied around the free end of the tendon. The thread was led over pulleys and attached to a myograph lever, the writing point of which was adjusted so as to record the contractions of the muscle upon a moving smoked surface. By means of an incision made in the midline of the posterior aspect of the thigh, the sciatic nerve was exposed between the hamstring muscles. The nerve was then crushed proximaly between the jaws of a pair of artery forceps, and a pair of shielded platinum electrodes were placed around the nerve distal to the crushed area. The nerve was stimulated using single shocks by means of a Dobbie McInnes square wave generator at a frequency of 8 per minute at 25 to 50 volts with the pulse width of 4 to 6 m.sec. The voltage and pulse width were of such magnitudes as to give supramaximal stimulation. In each experiment the frequency, voltage and pulse width were kept constant.

The following studies were made with this preparation:-

(1) <u>The effect of orphenadrine on the contracture and neuromuscular block induced by Suxamethonium.</u>

Control intravenous injections of 25 µg./kg. of Suxamethonium were given and the effects recorded. Orphenadrine 3.0 mg./kg. (although in some experiments 1 mg., 5 mg. and 6 mg. per kg. were also used) was given. Then Suxamethonium 25 µg. per kg. was given after about 10 minutes and the same dose repeated when the contractions had returned to their normal level.

(2) <u>The effect of orphenadrine on the neuro-muscular</u> /

(2) The effect of orphenadrine on the neuromuscular block induced by tubocurarine.

Control intravenous injections of from 200 to 300 µg. per kg. of tubocurarine were given. It was usual to give about three doses before the degree of neuromuscular block was constant. At least two standard records were obtained before orphenadrine 3 mg. per kg. was given intravenously. Tubocurarine 200 to 300 µg. per kg. was then given 5 to 10 minutes after giving orphenadrine and the same dose was repeated when the contractions had returned to normal. The dose of tubocurarine was constant in each experiment.

(3) The effect of orphenadrine on indirect tetanisation

The muscle was tetanised for 30 seconds at a frequency of 1400 to 1500 per minute every 10 to 15 minutes. Orphenadrine 3 mg. per kg. was given intravenously after two or three control records had been obtained. The frequency of the tetanising current and the period of rest between consecutive inductions of tetanus were kept constant in each experiment.

(4) The effect of orphenadrine on the fatigue induced by indirect tetanisation.

The degree of fatigue was assessed by measuring the height of contraction just before tetanisation and that just before the next tetanisation. The degree of fatigue was expressed as a percentage of the preceding height of contraction.

Drug solutions were injected into the rubber connection between the /

the vein cannula and the burette. Each injection was followed by an infusion of 3 ml. of physiological saline from the burette.

2. Cat Gastrocnemius - Sciatic Nerve Preparation

METHOD

Cats weighing between 2.0 and 3.5 kg. were anaesthetised with sodium pentobarbitone (60 mg. per kg.) given by intraperitoneal injection. Surgical anaesthesia was produced in 15 to 30 minutes.

The cat was then laid on its back; the legs were secured, and the head extended. The trachea was cannulated and this was usually connected to a Starling type of artificial respirator. One external jugular vein and one of the common carotid arteries was cannulated.

The left leg was prepared for indirect stimulation of the gastrocnemius muscle through the sciatic nerve in the manner described for the hen, except that the sciatic nerve was dissected from the lateral aspect of the thigh instead of the posterior aspect.

Supramaximal stimulation was employed using a voltage of between 25 and 60 volts and a pulse width of from 3 to 4 m.sec. The frequency of stimulation was about 8 per second. The voltage, pulse width and frequency of stimulation were kept constant for each experiment. When the effect of the drugs on tetanus was being studied, the frequency of the tetanising current was 1,600 per minute.

The following studies were carried out using this preparation:-

(1) /

(1) The effect of orphenadrine on the neuromuscular block induced by Suxamethonium.

Suxamethonium in doses ranging from 50 µg. to 150 µg. per kg. was used but the amount was constant for each experiment. At least two similar consecutive records were obtained as controls before orphenadrine was injected intravenously. The doses of orphenadrine used were 3.0 mg. and 5.0 mg. per kg. One to 2 minutes after injecting orphenadrine, a further dose of suxamethonium was injected and this was repeated when the contractions had returned to control levels.

(2) The effect of orphenadrine on the neuromuscular block induced by tubocurarine.

Tubocurarine 100 µg. to 150 µg. per kg. was used, but the dose was constant for each experiment. Intravenous injections of tubocurarine were repeated until the degree of neuromuscular block became constant. Orphenadrine was then injected intravenously. The doses of orphenadrine used were 3.0 mg. and 5.0 mg. per kg. About two minutes after giving orphenadrine, tubocurarine was given intravenously and the dose was repeated when the contractions had returned to control levels. In a few experiments, the effects of tubocurarine on indirect tetanisation were studied before and after giving orphenadrine.

(3) The effect of orphenadrine on indirect tetanisation

The muscle was tetanised for 30 seconds at a frequency of 1,600 impulses per second every fifteen minutes. Orphenadrine 3.0 to 5.0 mg. per kg. was given intravenously after at least two control records had /

had been obtained. The muscle was subsequently tetanised every fifteen minutes for an hour or longer. In some experiments up to 8 mg. per kg. of orphenadrine was used.

3. Experiments Using the Isolated Frog Rectus Abdominis Muscle

METHOD

The procedure used for preparing the muscle to record the effects of drugs was essentially similar to that described by Burn (1952). An adult frog was stunned by means of a blow on the head and was then pithed. The pithed frog was laid on its back upon a cork-covered dissecting board to which it was pinned. The rectus muscle was exposed by cutting away the skin of the abdomen. The muscle was then carefully dissected from the frog, and suspended in an organ bath of 10 ml. capacity by means of two threads tied one to either end of the muscle. A loop was made in the thread at one end in order to fix the muscle to the bent wire at the base of the bath. The longer thread attached to the other end was tied to a modified frontal point writing lever which gave a magnification of from 8 to 10 times. The bath (Fig. 55) contained 10 ml. of oxygenated frog Ringer's Solution (NaCl, 6.5g.; KCl, 0.14 g.; $CaCl_2$, 0.12 g., $NaH\ CO_3$, 0.2 g.; NaH_2PO_4 0.01 g., glucose, 2 g. to 1 litre of distilled water), at room temperature. Acetylcholine was dissolved in frog Ringer's solution to give the required /

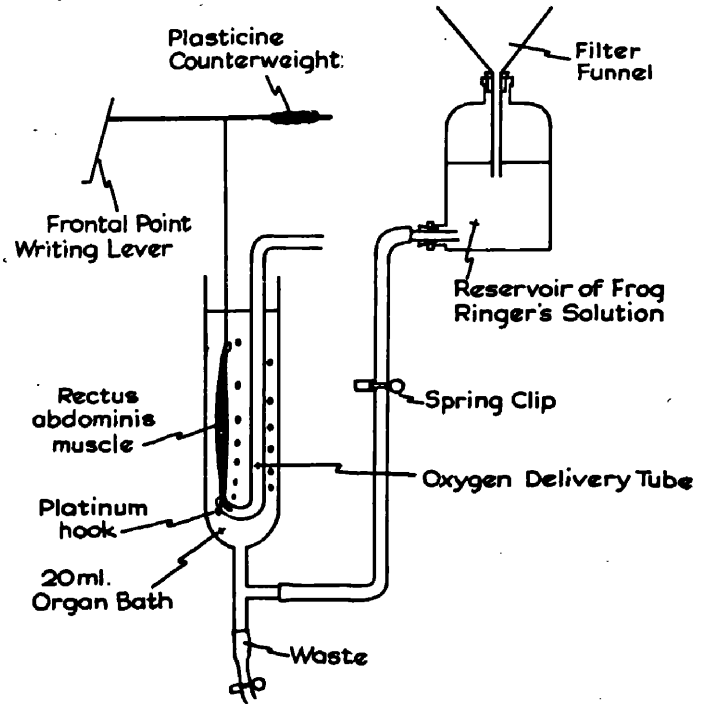


Fig. 55. Diagram of the apparatus used for experiments upon the isolated frog rectus abdominis muscle.

required concentration and added to the bath by means of a graduated 1 ml. tuberculin syringe. The final concentration of acetylcholine (in the bath) used to produce contractions of the muscle was from 1 to 3 µg. per ml.

Uniform submaximal contractions to the same dose of acetylcholine were obtained before the effects of orphenadrine were studied. The time interval between each dose of acetylcholine was four minutes. The resulting contractions were recorded for 45 seconds and the bath was washed out between each dose of acetylcholine. Orphenadrine to give a final bath concentration of from 5 µg. to 25 µg. per ml. was added 15 seconds before the acetylcholine. In some experiments the effects of tubocurarine were compared with those of orphenadrine and in others the effect of adding tubocurarine and orphenadrine together was studied. Tubocurarine was added to the bath 15 seconds before acetylcholine.

4. Experiments Using the Isolated Rat Phrenic Nerve Diaphragm Preparation.

METHOD

The procedure adopted was essentially that described by Bülbring (1946). Adult rats of either sex were killed by a blow on the head, the throat cut and the blood allowed to drain out. The rat was then laid on its back upon a cork-covered dissecting board to which it was pinned. The skin over the chest was removed and the thorax opened along the left hand side of the sternum. The frontal part of the left thoracic /

thoracic wall was removed and the phrenic nerve exposed. Left-sided pneumonectomy was performed and the left phrenic nerve carefully freed from fat and other tissues. The utmost care was taken not to injure it. The left anterior abdominal muscles were cut along the costal margin and, holding the last rib with a pair of forceps, a segment of the diaphragm was dissected out. Two converging cuts were made through the ribs towards the tendinous part of the diaphragm, and parallel to the direction of its muscle fibres. The cuts were made so that the point of entry of the phrenic nerve into the diaphragm lay in the middle of this segment. The strip of diaphragm was dissected out beyond its tendinous part with about 5 cm. of phrenic nerve attached to it. The final preparation was fan-shaped, being about 2 mm. wide at the tendinous end and about 2 cm. wide at the costal margin. The costal margin of the segment of diaphragm was fixed to a J-shaped glass rod by means of threads. The thread was stitched on to the tip of the tendinous end. In experiments where both direct and indirect stimulation were to be used, fine platinum wires instead of thread were used for the tendinous end. The preparation was then set up in a 100 ml. organ bath (Fig. 56) containing double glucose Tyrode's solution (NaCl, 8 g.; KCl, 2 g.; $CaCl_2$, 0.2 g.; $MgCl_2$, 0.1 g.; $NaHCO_3$, 1 g.; NaH_2PO_4, 0.05 g.; glucose 2 g.; to 1 litre of distilled water). The J-piece held the costal margin of the segment in position at the bottom of the organ bath while the thread or the platinum wire tied at the tendinous end was fixed to a light isotonic heart lever writing upon a revolving /

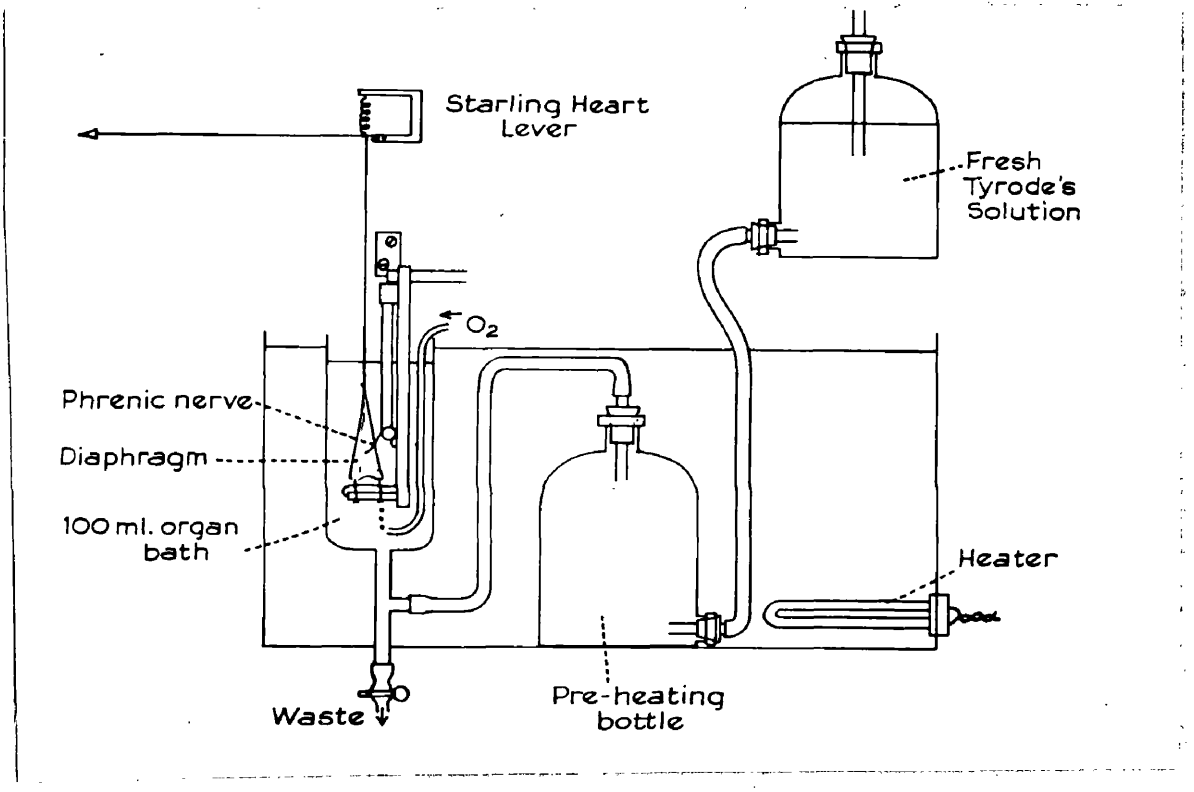


Fig. 56. Diagram of the apparatus used for recording contractions of the rat diaphragm produced by electrical stimulation of the phrenic nerve.

revolving smoked surface. Tyrode's solution was supplied to the bath from a reservoir. The temperature of the bath and the reservoir was maintained thermostatically at 29 ± 0.5°C. A sintered glass distribution tube was fixed at the bottom of the bath to provide a vigorous supply of oxygen with which the organ bath fluid was aerated in the form of fine bubbles. The phrenic nerve was stimulated using the electrode described by Bell (1952) so that the muscle could be stimulated both directly and indirectly. Stimulation of the nerve was by square impulses at a frequency of from 6 to 8 per minute, 10 to 15 volts and a pulse width of 0.5 to 1.0 m.sec. When the muscle was stimulated directly the frequency was from 6 to 8 per minute at 30 to 50 volts and the pulse width was 1.5 to 2.0 m.sec. In any given experiment, frequency, voltage and pulse width were kept constant. Drugs in aqueous solution were added directly to the bath by means of a 1 ml. tuberculin syringe. The drug was allowed to act for three minutes after which the Tyrode's solution in the bath was changed. The bath was washed out several times with the Tyrode's solution in between additions of the drugs. Additions of drugs were made when the contractions had recovered to the original size or reached a new but steady level. This meant in some instances an interval between additions of drugs as long as 80 minutes.

Chou (1947) using the phrenic nerve diaphragm preparation for the assay of curare-like substances, allowed the solution of tubocurarine to act for three minutes. In the experiments described in this section, /

section, this feature of Chou's technique was therefore adopted because it was thought that if the drug was allowed to act upon the tissue for long enough to produce its maximal effect then too much time would be needed to wash the drug off the receptors.

5. Experiments on the effect of Orphenadrine on Spinal Reflexes - Patellar Reflex and the Crossed Extensor Reflex

METHOD

Cats weighing between 2.0 kg. and 5.5 kg. were used. Anaesthesia was induced as previously described (page 281).

The anaesthetised cat was laid on its back upon an operating table. The trachea was cannulated and connected to a Starling type of artificial respirator. The two common carotid arteries were ligatured high in the neck. The cat was then turned over and an incision made in the midline from the top of the head to the shoulders. The muscles were freed from the vertebral column and the vertebral arteries were ligatured by means of a strong thread passed between the second and third cervical vertebrae. The atlanto-occipital ligament was then incised in the midline and a probe passed through the foramen magnum into the cranial cavity to destroy the brain. It was also passed downwards to destroy the upper one or two segments of the spinal cord. Bleeding was controlled by the use of very hot saline packs.

The /

The cat was again turned on its back and its legs secured. The external jugular vein on the left side was cannulated and connected to a 50 ml. burette containing physiological saline. The right carotid artery was cannulated and connected to a mercury manometer and the blood pressure recorded on a revolving smoked surface. The next stage was dependent on the reflex to be studied.

(a) The patellar reflex - knee jerks. The left limb was flexed at the knee. The posterior aspect of the knee was made to rest on a horizontal brass bar and between two X-blocks. The position of the leg was fixed more securely by means of two strong linen threads stitched through either side of the upper part of the leg and tied securely to another horizontal brass bar above the knee. (These horizontal bars were secured by X-blocks to fixed vertical stands on the table.)

The skin in front of the knee was excised to expose the patellar tendon. A very small incision was made on either side of the tendon to allow a pair of platinum electrodes to be placed under the tendon but without allowing free movement of the electrodes under it. A strong linen thread was stitched to the front of the foot in the mid-line. The thread was led over pulleys and attached to a myograph lever, the writing point of which was adjusted so as to record the contractions of the muscle upon a moving smoked surface.

The patellar tendon was stimulated using single shocks from a square wave generator at a frequency of about 6 per second, at 25 to

60 /

60 volts and a pulse width of 1.5 to 3.5 m.second. In any one experiment, the reflexes were elicited for two or three minutes with a rest period of three minutes in between. In one experiment the frequency of stimulation was 3 per minute and the reflexes were elicited continuously.

(b) The Crossed Extensor Reflex. The left hind limb was flexed at the knee and the posterior aspect of the knee was made to rest on a horizontal brass bar and held between two metallic blocks. The skin in front of the knee was excised to expose the patellar tendon. The tendon was severed from its insertion into the tubercle of the tibia and dissected free from the surrounding tissues. A strong linen thread was tied around the free end of the tendon, led over pulleys and attached to a myograph lever, the writing point of which was adjusted so as to record the contractions of the quadriceps muscle upon a moving smoked surface. The right hind limb was then prepared for stimulation of the sciatic nerve to produce the crossed extensor reflex (contraction of the left quadriceps muscle). The leg was held with its long axis perpendicular to the operating table by tying it with strings to a perpindicular metal bar fixed to the table. By means of an incision made on the lateral aspect of the thigh the sciatic nerve was exposed between the hamstring muscles. The distal portion of the nerve was crushed between the jaws of a pair of artery forceps and a pair of shielded platinum electrodes placed around the nerve proximal to the crushed area. This means that nerve impulses from the sciatic nerve /

nerve will be conducted to the spinal cord instead of to the calf muscles.

The right sciatic nerve was stimulated to produce supramaximal contractions of the left quadriceps muscle (crossed extensor reflex). Single shocks from a square wave generator at a frequency of between 6 and 10 per minute at 10 to 40 volts and a pulse width of 1.5 to 3.5 m.sec. were used. In each experiment the frequency, voltage and pulse width were kept constant. In all the experiments the reflexes were elicited for 3 to 5 minutes with a rest period of from 3 to 5 minutes. In each experiment the periods when the reflexes were elicited and the periods of rest were kept constant. Rest periods were introduced because it was thought that fatigue might set in if the reflexes were elicited continuously every 6 to 10 seconds and it might be impossible to differentiate between depression of the reflex by the drug and fatigue of the reflex.

Orphenadrine was given intravenously in the dose of 1 mg., 3 mg. or 5 mg. per kg. In later experiments the initial 1 mg. per kg. dose was omitted as it was found to have no effect on the two types of reflexes. Each injection of orphenadrine was followed as usual by an infusion of 3 ml. of physiological saline. At least two control records were obtained before the orphenadrine was injected.

6. Experiments on the Blood Pressure of the Anaesthetised Cat

METHOD

Cats /

METHOD

Cats of either sex weighing between 1.5 and 3 kg. were used. Anaesthesia was induced by means of intraperitoneal injection of sodium pentobarbitone 50 mg. to 60 mg. per kg. This produced surgical anaesthesia in about 20 to 30 minutes.

The anaesthetised cat was laid on its back upon an operating table. The legs were secured to the table and the head extended by a string attaching the upper incisor teeth to the table. The skin covering the neck was cut away from the sternum up to the apex of the mandible. The trachea was exposed by blunt dissection. A strong linen thread was passed around the trachea which was then incised transversely. The cut edge of the partly severed trachea was held in a pair of blunt forceps and a tracheal cannula inserted and tied into place. The insertion of a tracheal cannula was done as a precautionary measure so that if severe drug-induced respiratory depression or failure occurred the cat could be kept alive by means of artificial respiration. The amount of air entering and leaving the cannula was controlled by means of an adjustable valve.

One external jugular vein, usually the left, was then cannulated. To do this the skin of the left anterior part of the neck was removed and the vein exposed by blunt dissection. The fascia covering the vein was carefully removed, two threads were tied loosely around the vein and a bulldog clip put on to the cardiac aspect of the vein and tied off at the cephalic end. A small transverse incision was made in the /

the dilated vein by means of a pair of sharp-pointed iris scissors. A vein cannula filled with a solution of heparin was then inserted through the incision with the pointed end towards the heart. The lower thread was now used to secure the cannula in the vein. The cannula was then connected by means of a rubber tubing to a 50 ml. burette containing normal physiological saline. Care was taken to exclude all air bubbles from the system. The bulldog clip was then removed. If, when the clip on the rubber tubing was released, the saline in the burette ran freely into the vein, then the cannula had been correctly inserted.

The next step was to cannulate the artery. The artery was first tied off as near to the head as possible. A bulldog clip was then placed on the artery about 3 cm. below the ligature and a second thread was passed under the vessel approximately midway between the ligature and the bulldog clip. A small transverse cut was made in the artery by means of a pair of sharp-pointed scissors. An artery cannula filled with a solution of heparin was then inserted through the incision with the pointed end towards the heart. The cannula was connected to a mercury manometer and the space between the mercury and the cannula filled with a twenty-five per cent (w/v) solution of sodium thiosulphate as an anticoagulant. In some experiments physiological saline to which heparin had been added (to give 1 : 200 solution) was used. All air in the tube containing the anticoagulant solution was displaced and the pressure in the manometer was set at about 100 to 120 mm. /

120 mm. of mercury before connecting the cannula to the manometer. A writing flag on one arm of the mercury manometer recorded the blood pressure on a smoked drum.

Drug solutions were injected into the rubber connection between the vein cannula and the burette. Each injection was followed by infusion of 3 ml. of saline from the burette. The effect of orphenadrine 3.0 mg. per kg. and 5.0 mg. per kg. on the blood pressure and in some cats on the pressor response to adrenaline 4.0 to 8 ug. and noradrenaline 4.0 to 8 ug. was studied. Orphenadrine was dissolved in physiological saline to give a solution containing 20 mg. per ml.

7. Experiments on the Blood Pressure of Spinal Cats

METHOD

Cats of either sex weighing between 2 and 4 kg. were used. Anaesthesia was induced by means of intraperitoneal injection of sodium thiopentone (50 mg. per kg.). This produced surgical anaesthesia in about 20 to 30 minutes.

The common carotid arteries were dissected from the accompanying vagosympathetic trunks and tied. The trachea was next freed from the adjoining tissues, cannulated and connected to the artificial respiration pump (with the valve of the trachea cannula wide open). The cat was then turned over and then spinalised as described on page 289. As soon as the cord was transected, the valve of the trachea cannula was regulated /

regulated so that adequate pulmonary ventilation was obtained. The cat was then turned on its back and the left external jugular vein cannulated and connected to a 50 ml. burette by a short rubber tube. The right common carotid artery was then cannulated and connected to the mercury manometer as already described. The pressure of the mercury manometer was set at about 80 mm. of mercury before the arterial cannula was connected to the manometer. The blood pressure was recorded on a smoked surface.

Drug solutions were injected into the rubber connection between the vein cannula and the burette. Each injection was followed by the infusion of 3 ml. of saline from the burette.

A period of at least 45 minutes was allowed for the blood pressure to attain a fairly constant level and no drugs were given until this level had been maintained for 25 to 20 minutes.

8. Experiments on the Nictitating Membrane of the Anaesthetised Cat

This study was made to find out if the fall in blood pressure produced by injection of orphenadrine was due to a sympathetic ganglion blocking effect.

METHOD

Cats of either sex weighing between 3 kg. and 5 kg. were used. The cat was anaesthetised as already described with sodium pentobarbitone. /

pentobarbitone. The trachea and the external jugular vein were cannulated and the vein cannula connected to a 50 ml. burette. The left internal carotid artery was cannulated and connected to mercury manometer. The head was rigidly fixed by passing a brass rod between the jaws and then tying the jaws firmly together with string. The ends of the rod were then gripped firmly in clamps and these were supported on uprights fixed to the side of the operating table. By means of a fine needle, a silk thread was passed through the midpoint of the margin of the nictitating membrane of the right eye and tied firmly into place. The thread was then pulled forward and to one side making an angle of about 30° to the long axis of the cat. It was then led around pulleys and attached to a frontal-point writing lever. The contractions of the nictitating membrane and the blood pressure were recorded on a smoked surface.

The right cervical sympathetic chain was dissected out, and a fine cotton thread tied tightly around it as low down in the neck as possible. The sympathetic chain was severed just below the ligature. The cut preganglionic cervical chain was placed upon a pair of platinum electrodes kept moist with normal saline. Contractions of the nictitating membrane were elicited by stimulation of the cervical sympathetic chain by means of square wave impulses at a frequency of 1,200 per minute, 20 volts and amplitude and a pulse width of 1.5m.sec. The nerve was stimulated at 3 minute intervals for 5 to 10 seconds. The period of stimulation was kept constant for each experiment. Having obtained

about /

about six standard reproducible responses of the nictitating membrane, a solution of orphenadrine 3.0 or 5.0 mg. per kg. was injected into the external jugular vein about 30 seconds before the next period of stimulation. The effects of ethopropazine 5.0 mg. per kg. and hexamethonium 1.5 to 2.0 mg. per kg. were also studied.

9. Experiments on the Isolated Perfused Rat Hindquarters.

This experiment was embarked upon in order to try to explain the hypotensive effect of orphenadrine. It was thought that this may be due to a widespread vasodilatation. It was also performed in order to find out if the dissipation of fatigue by orphenadrine was due to a possible vasodilator effect.

METHOD

In these experiments, the pressure at which the physiological fluid passed through the blood vessels was kept constant. The drug-induced alterations in the rate of outflow of the perfusion fluid were recorded by means of a Thorpe drop recorder. The vessels were perfused with oxygenated Locke's solution (NaCl, 9 g.; KCl, 0.42 g.; $CaCl_2$, 0.24 g.; $NaHCO_3$, 0.5 g.; glucose 1 g. to 1 litre of distilled water), at room temperature.

Rats of either sex weighing between 200 and 300 g. were killed by

a /

a blow on the head. The throats were cut and the blood allowed to drain out. The abdominal cavity was opened by means of a longitudinal incision extending from the sternum to the anus and the rectum, oesophagus and the inferior and superior mesenteric arteries divided between ligatures. The abdominal viscera were then removed and this brought into view the abdominal aorta which was cannulated. The body wall and vertebral column were transected above the point of cannulation, the cannula was filled with heparin and connected to the perfusion system (Fig. 57) by means of fine rubber tubing. The hindquarters preparation was placed on a muslin rest lying in a filter funnel and the outflow was led *via* the filter funnel over the contacts of the Thorpe drop recording assembly.

The rate of flow of fluid to the injection cannula was controlled by a tap and could be adjusted to a suitable rate value at the beginning of each experiment. The injection cannula (the design of which was based upon that suggested by Gaddum and Kwiatkowski, 1938) allowed the drug solutions to be injected at a constant rate. This was achieved by injecting the solution through the rubber cap at a rate such that the level of fluid in the cannula was unaltered during the process.

After setting up the preparation, a uniform outflow record was obtained for at least 10 minutes before drugs were injected. The effects of adrenaline 0.25 µg. to 1 ug. and noradrenaline 1 µg. to 3 µg. were compared with those of orphenadrine 25 µg. to 250 µg. (0.1 ml. of orphenadrine solution was used in all instances). The

effect /

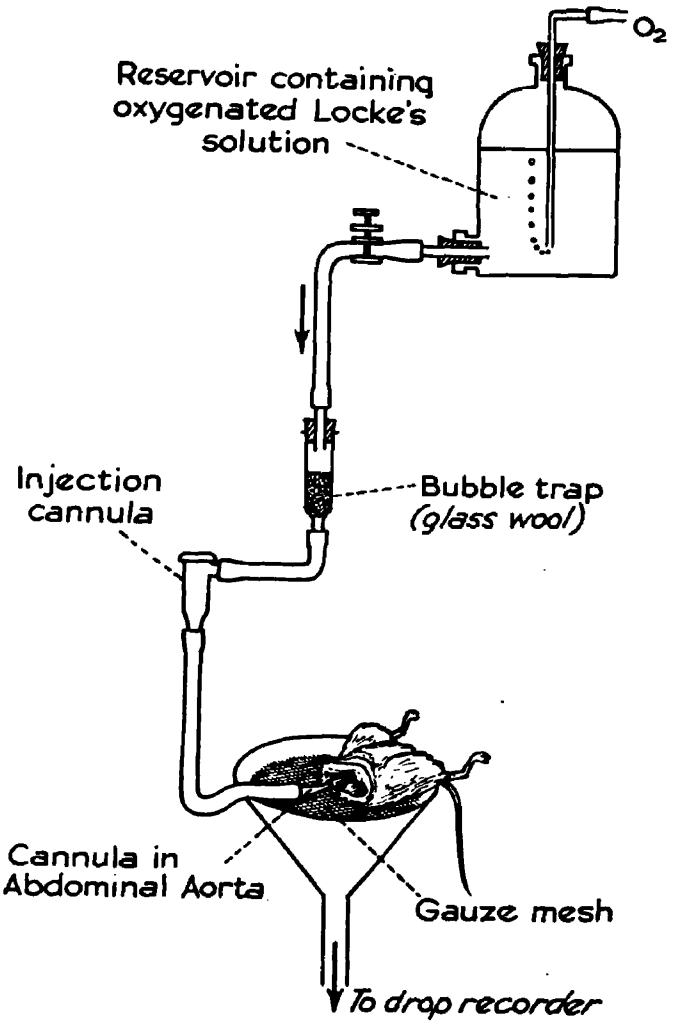


Fig. 57. Diagram of the apparatus used for the perfusion of the isolated rat's hindquarters.

effect of previous administration of orphenadrine on the vasoconstrictor response to adrenaline and noradrenaline was studied. The effect of previous administration of Tolazine on the vasoconstrictor action of orphenadrine and noradrenaline was also studied in a few experiments.

10. Effect of Orphenadrine on the Convulsant Activity of Leptazol

Female albino mice weighing between 18 and 26 g. were used in the experiments. The mice were divided into groups each containing at least 10 mice. Four control groups received leptazol alone; each group receiving either 20 mg., 30 mg., 40 mg., or 60 mg. per kg. The other groups were pretreated with orphenadrine at doe levels of 1 mg., 3 mg. and 15 mg. per kg. Leptazol was then injected 25 to 40 minutes after injecting orphenadrine. Aqueous solutions of leptazol and orphenadrine were used, and the solutions were injected into one of the tail veins. The volume of the solution of leptazol or orphenadrine was kept constant irrespective of the dose level and the duration of injection did not exceed three seconds. In order to carry out the experiment the movements of the mouse were restricted by placing it in a small metal cylinder, one end of which was perforated to allow exposure of the tail. In order to render the tail vein more visible, the tail was wiped with a swab of cotton wool soaked in xylene. The number of mice convulsing after injecting leptazol was recorded. The mortality rate from leptazol was also recorded.

11. Effect of Orphenadrine on Electroshock Seizures

The apparatus was similar to that employed by Ahmad and Lewis (1960) who used the ear clip electrodes introduced by Hoyt and Rosvold (1951). Four groups of 20 female albino mice weighing between 15 and 21 g. were used. Because it was thought that orphenadrine had a convulsant action of its own, supramaximal threshold current intensity of 20mA was not used in earlier experiments when the effect of 3 mg. and 12 mg. of orphenadrine per kg. was studied. The current intensity was 17mA. In the other two groups who received 6 mg. and 15 mg. of orphenadrine per kg. body weight respectively, the supramaximal threshold current intensity of 20mA. was used. The current was allowed to act for not more than 5 seconds although it was interrupted earlier, if it produced tonic extension of the hind limbs (which was regarded as the end point). Twenty-four hours before the effects of pretreatment with orphenadrine on electroshock seizures were studied, the number of mice in each untreated group giving a positive reaction, i.e., showing the end point, was noted. The next day the mice were treated with orphenadrine injected intravenously into a tail vein at dose levels of 3 mg., 6 mg., 12 mg. and 15 mg. per Kg. 25 to 35 minutes later, electroshock was applied using a current of the same intensity and duration as stated above. The number showing the end point (positive reactors) was again noted.

RESULTS

1. Hen Gastrocnemius Muscle - Sciatic Nerve Preparation.

(a) Effect of orphenadrine on the contracture (muscular spasm) induced by suxamethonium

In 3 out of 8 hens, orphenadrine at a dose of 3.0 mg. per kg. diminished the degree and duration of the contracture produced by suxamethonium. Orphenadrine at this dose itself caused neuromuscular block in one of the 8 hens; the block lasting for 20 minutes (Fig.59). In 6 of the 8 hens, pretreatment with orphenadrine (3 and 5 mg. per kg.) caused an increase in the degree and duration of the neuromuscular block induced by a given dose of suxamethonium (12.5 to 25 µg. per kg.). In 3 hens prolonged complete neuromuscular block occurred and in one instance it took about 33 minutes before the height of the muscle contractions returned to the pre-injection level (Fig. 59). In 2 preparations, 60 and 90 µg. per kg. of Neostigmine (prostigmin) antagonised the neuromuscular block induced by suxamethonium after pretreatment with orphenadrine (Figs. 58 and 60).

(b) Effect of orphenadrine on neuromuscular block induced by tubocurarine.

Pretreatment with orphenadrine 3 mg. per kg. caused an increase in the degree of neuromuscular block induced by a constant dose of tubocurarine. /

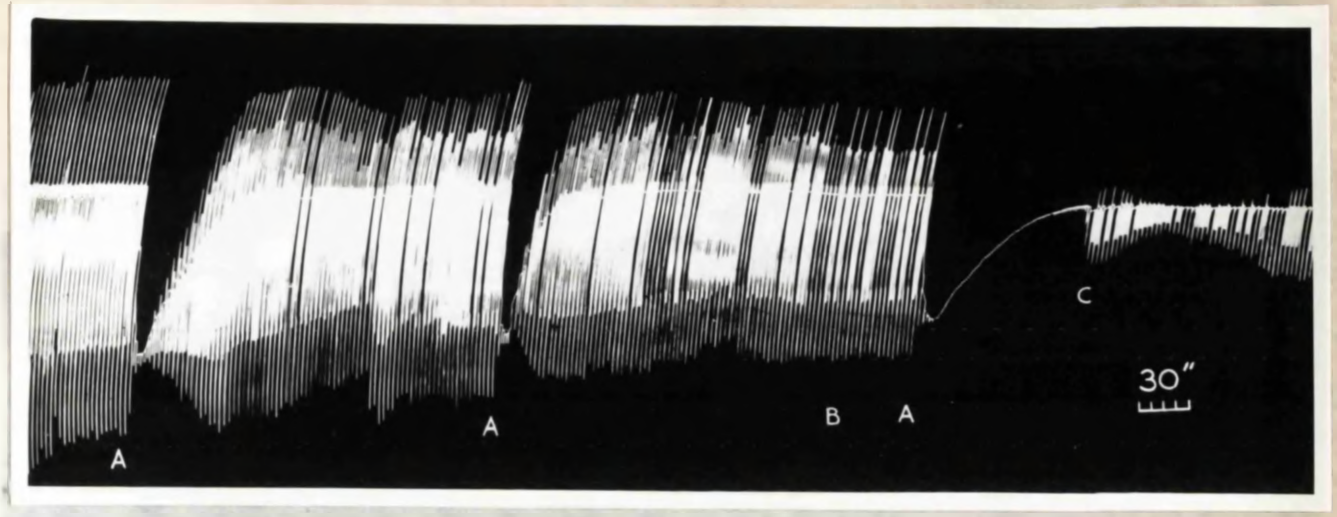


Fig. 58. Hen gastrocnemius muscle - sciatic nerve preparation. Pentobarbitone anaesthesia. Indirect stimulation via the sciatic nerve. Contractions downwards. Drugs administered intravenously.

At A, Suxamethonium 12.5 µg. per kg.

At B, Orphenadrine 3.0 mg. per kg.

At C, Neostigmine 90 µg. per kg.

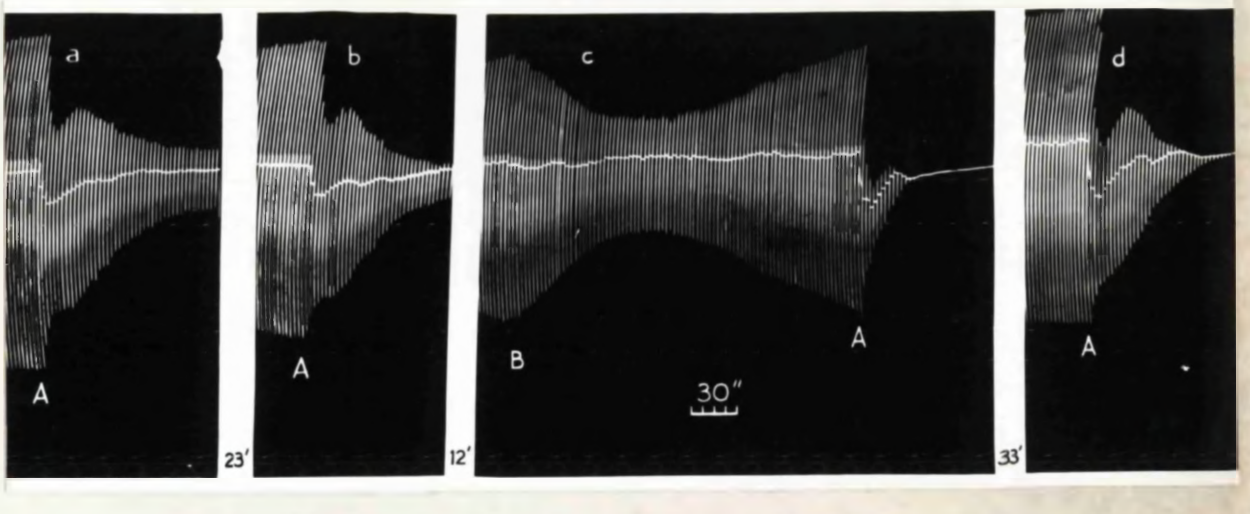


Fig. 59. Hen gastrocnemius muscle - sciatic nerve preparation. Pentobarbitone anaesthesia. Indirect stimulation via the sciatic nerve. Contractions downwards. Drugs administered intravenously.

At A, Suxamethonium 25 µg. per kg.

At B, Orphenadrine 3.0 mg. per kg.

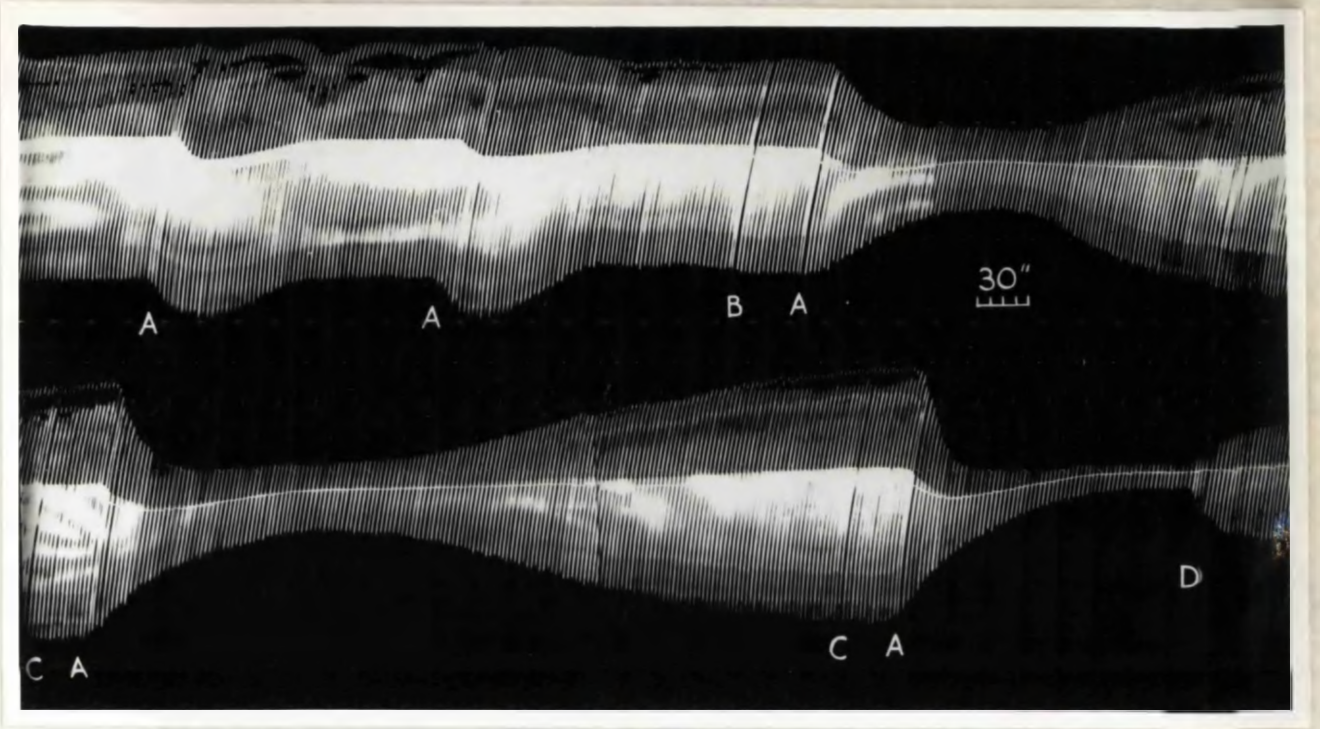


Fig. 60. Hen gastrocnemius muscle-sciatic nerve preparations. Pentobarbitone anaesthesia. Indirect stimulation via the sciatic nerve. Contractions downwards. Drugs administered intravenously.

At A, suxamethonium 25 µg. per kg.

At B, orphenadrine 3.0 mg. per kg.

At C, orphenadrine 5.0 mg. per kg.

At D, neostigmine 60 ug. per kg.

tubocurarine. The amplitude and duration of the block were increased although in a few instances only the duration of the neuromuscular block was significantly increased. Thus in one hen, 200 µg. per kg. of tubocurarine given intravenously produced a 25 to 30% neuromuscular block. After pretreatment with orphenadrine (3 mg. per kg.) the same dose of tubocurarine produced about 50% neuromuscular block (Fig. 61).

(c) Effect of orphenadrine on the response to indirect tetanisation and on fatigue

Orphenadrine 3.0 mg. per kg. was found to have no influence on the response of the gastrocnemius muscle to indirect tetanisation. The tetanic contraction was as well sustained as in the period before treatment with orphenadrine (Fig. 62). Orphenadrine however reduced the fatigue due to repeated indirect tetanisation. Thus in four hens, the average reduction in twitch height after indirect tetanisation was 22% before they received orphenadrine. After treatment with orphenadrine this was reduced to 5% (Table 24).

2. Cat Gastrocnemius Muscle - Sciatic Nerve Preparation.

(a) Effect of orphenadrine on neuromuscular block induced by suxamethonium.

Orphenadrine 3.0 mg. to 6.0 mg. per kg. while not producing any block of its own, considerably antagonised the neuromuscular block induced /

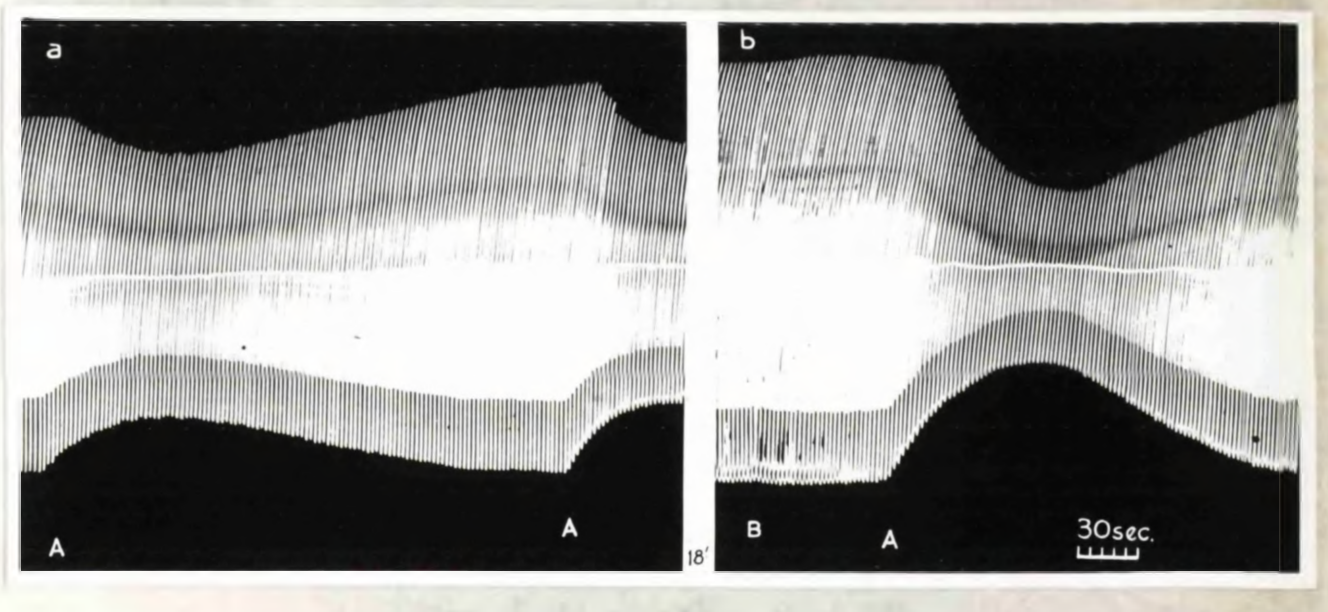


Fig. 61. Hen gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Indirect stimulation via the sciatic nerve. Contractions downwards. Drugs administered intravenously.

At A, tubocurarine 200 µg. per kg.

At B, orphenadrine 3.0 mg. per kg.

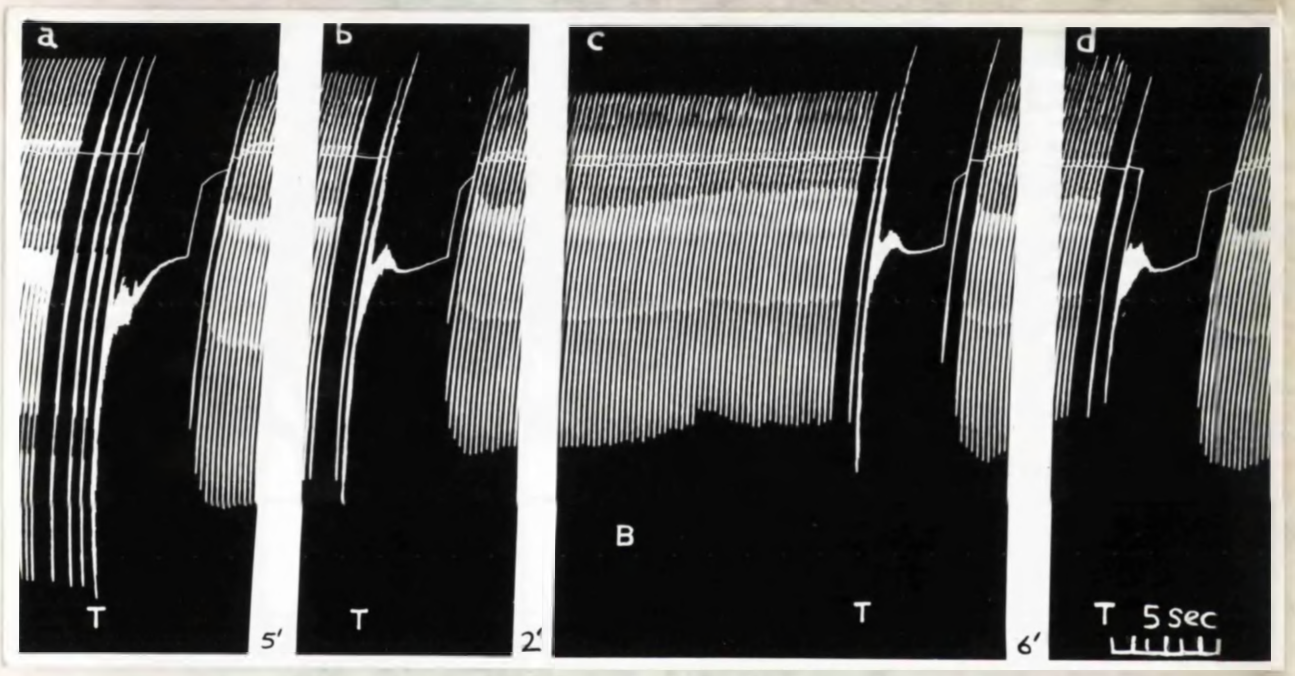


Fig. 62. Hen gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Contractions downwards. Drugs administered intravenously.

At T, indirect tetanisation via the sciatic nerve (1,500 impulses per minute).

At B, orphenadrine 3.0 mg. per kg.

Percentage Reduction in Twitch Tension

	Before Orphenadrine		*After Orphenadrine 3mg/kg*		
I	19·6	19·7	7·8	3·8	1·3
II	35	29	0	0	0
III	15·1	20·6	6·2	+8·5	6
IV	23·3	14·7	7·5	0	7
Average	22·4		5·6		

TABLE 24. Effect of orphenadrine 3 mg. per kg. given intravenously on the fatigue-induced after tetanisation of the sciatic nerve-gastrocnemius preparation of the hen.

induced by suxamethonium (Figs. 63 and 64). This antagonism was seen whether the block was complete or partial. In one cat, muscular spasm induced by suxamethonium (50 µg. per kg.) in the gastrocnemius muscle was very considerably reduced after treatment with orphenadrine 3.0 mg. to 6.0 mg. per kg. There was no change in the degree of neuromuscular block after indirect tetanisation indicating that although pretreatment with orphenadrine had reduced the degree of neuromuscular block induced by suxamethonium, the block was still of the depolarising type (Fig. 65).

(b) Effect of orphenadrine on neuromuscular block induced by tubocurarine

Pretreatment with orphenadrine 3.0 mg. to 5.0 mg. per kg. increased the degree of neuromuscular block induced by a given dose of tubocurarine. The amplitude and the duration of the neuromuscular block were increased (Fig. 66). The effect of indirect tetanisation on the neuromuscular block induced by tubocurarine was unchanged by orphenadrine; there was a transient decurarisation of the block induced by 100 µg. to 150 µg. per kg. of tubocurarine by indirect tetanisation of the gastrocnemius muscle both before and after treatment with orphenadrine (Fig. 67).

(c) Effect of orphenadrine on indirect tetanisation.

Orphenadrine 3.0 mg. to 5.0 mg. per kg. had no effect on the response of the gastrocnemius muscle to indirect tetanisation (Fig.68).

The /

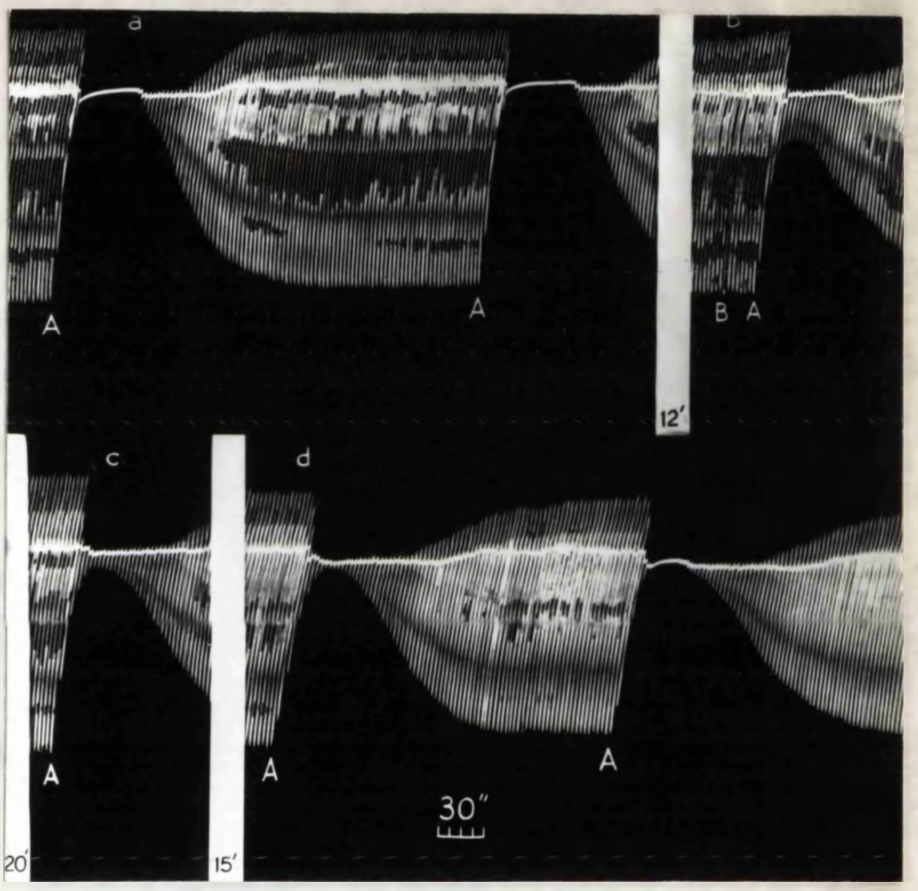


Fig. 63. Cat gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Indirect stimulation via the sciatic nerve. Contractions downwards. Drugs administered intravenously.

At A, suxamethonium, 150 µg. per kg.

At B, orphenadrine, 5.0 mg. per kg.

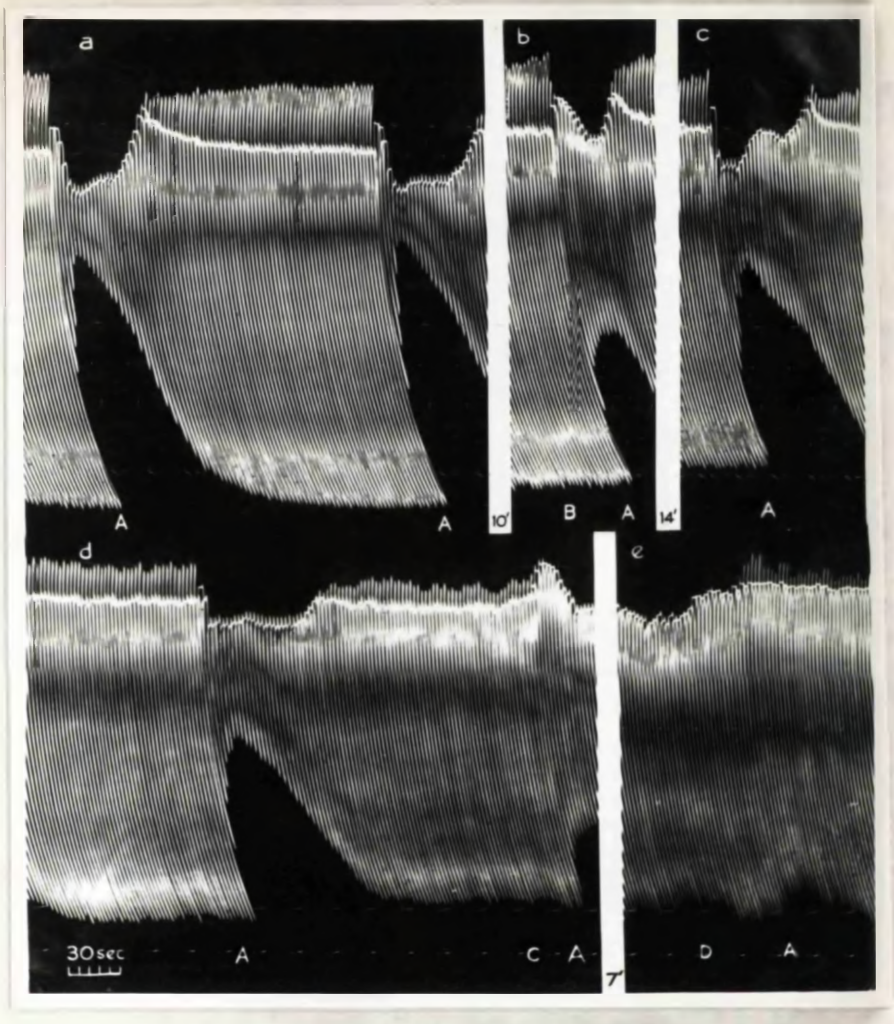


Fig. 64. Cat gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Indirect stimulation via the sciatic nerve. Contractions downwards Drugs administered intravenously.

At A, suxamethonium 50 μg. per kg.
At B, orphenadrine, 3.0 mg. per kg.
At C, orphenadrine, 5.0 mg. per kg.
At D, orphenadrine, 6.0 mg. per kg.

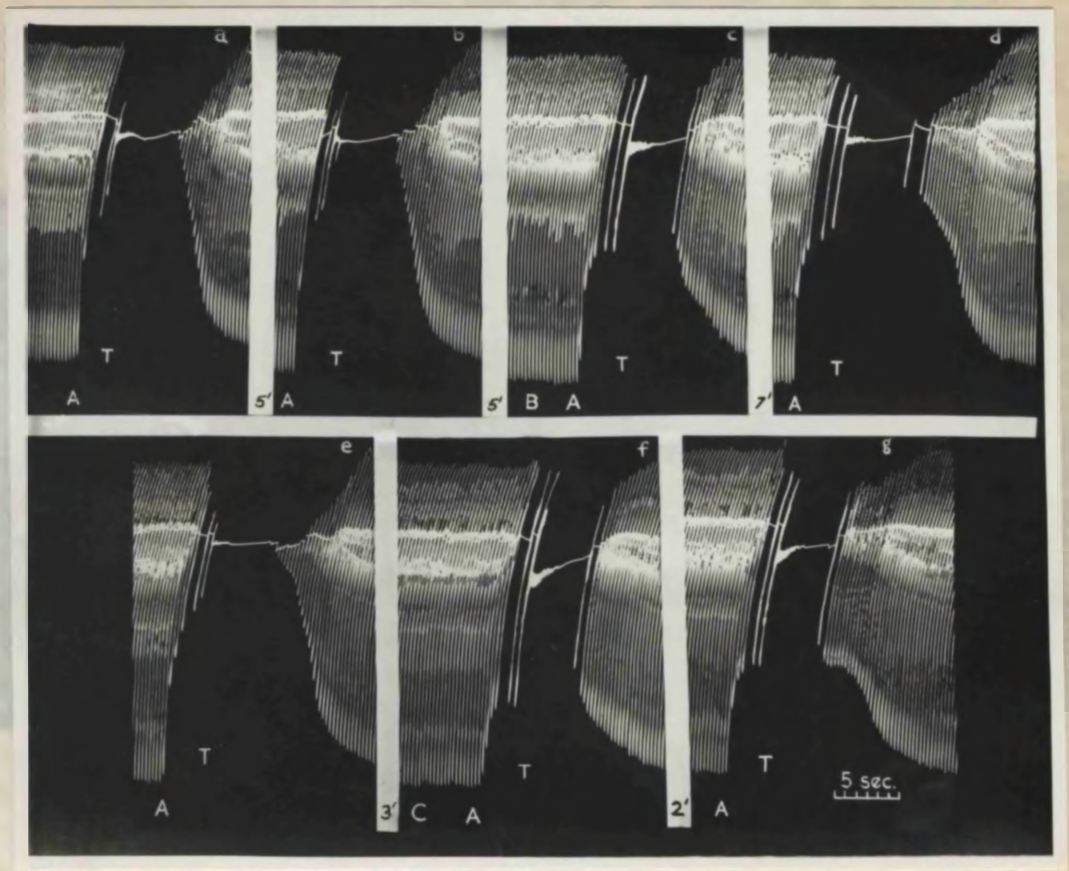


Fig. 65. Cat gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Contractions downwards. Drugs administered intravenously.

At T, indirect tetanisation via the sciatic nerve (1,500 impulses per minute).

At A, suxamethonium 100 µg. per kg.

At B, orphenadrine, 3.0 mg. per kg.

At C, orphenadrine, 6.0 mg. per kg.

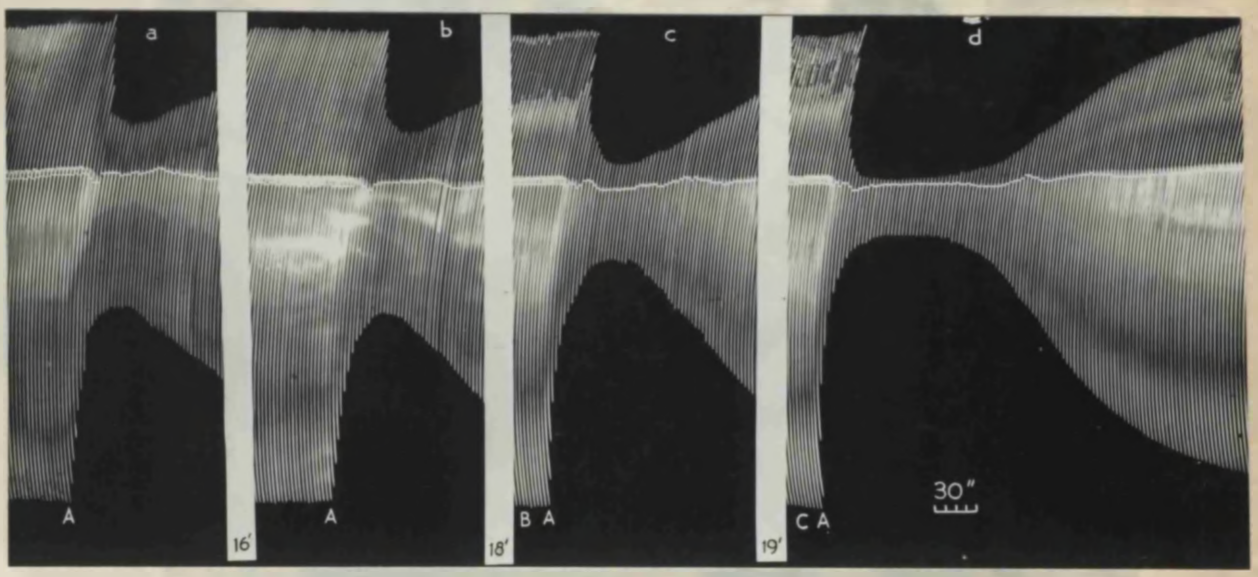


Fig. 66. Cat gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Indirect stimulation via the sciatic nerve. Contractions downwards. Drugs administered intravenously.

At A, tubocurarine 150 µg. per kg.

At B, orphenadrine 3.0 mg. per kg.

At C, orphenadrine 5.0 mg. per kg.

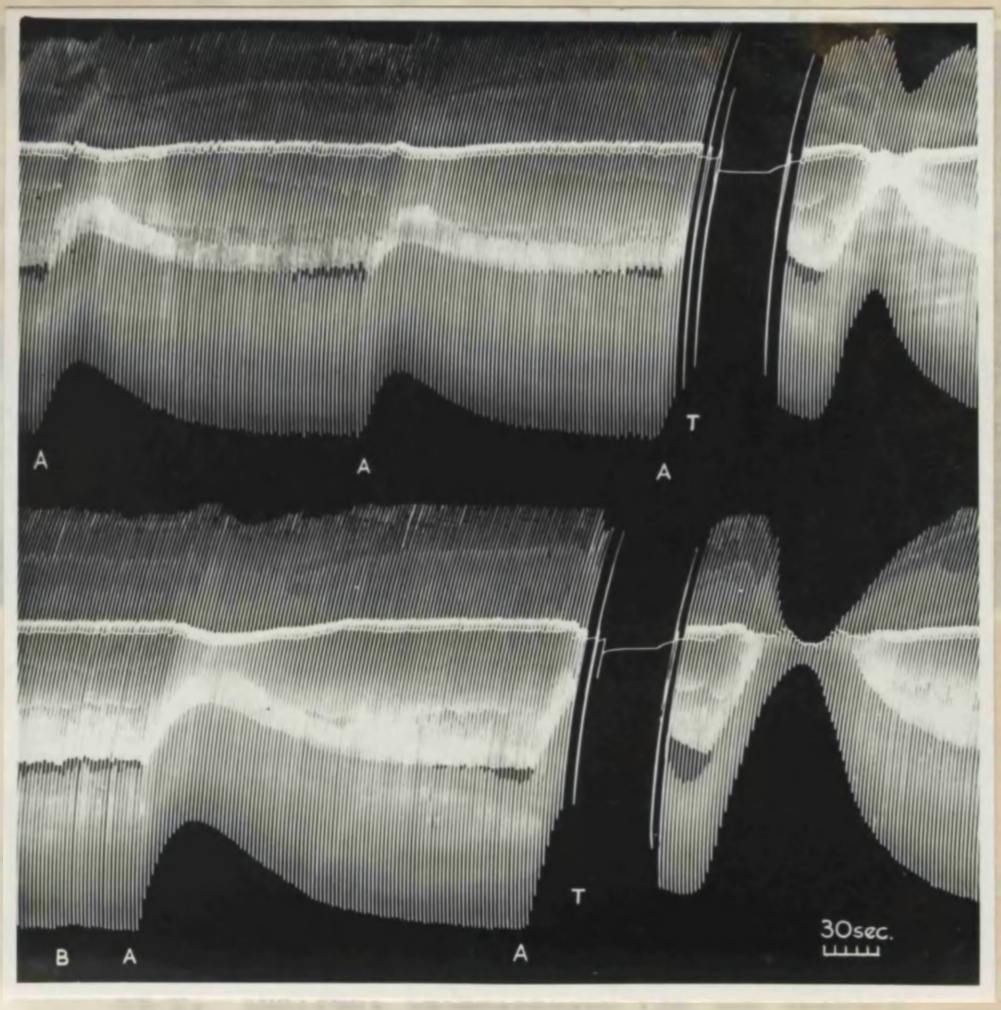


Fig. 67. Cat gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Contractions downwards. Drugs administered intravenously.

At T, indirect tetanisation via the sciatic nerve (1,500 impulses per minute).

At A, tubocurarine 100 µg. per kg.

At B, orphenadrine, 5 mg. per kg.

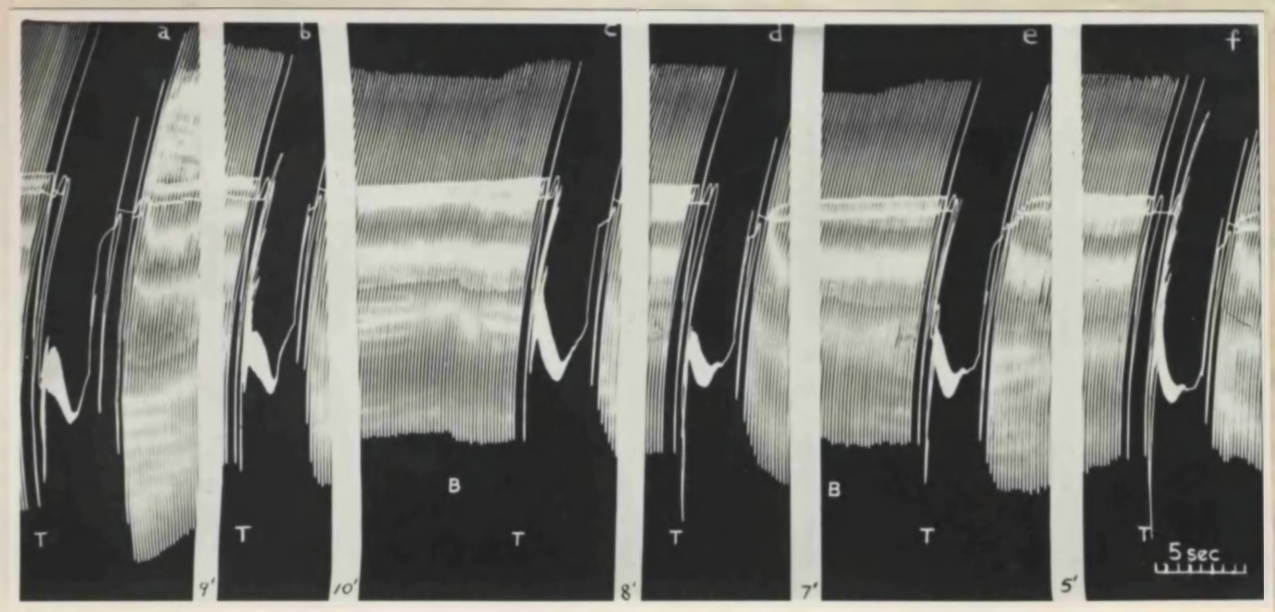


Fig. 68. Cat gastrocnemius muscle-sciatic nerve preparation. Pentobarbitone anaesthesia. Contractions downwards. Drugs administered intravenously.

At T, indirect tetanisation via the sciatic nerve (1,600 impulses per minute).

At B, orphenadrine 3.0 mg. per kg.

The tetanic contraction was as well sustained as in the period before treatment with orphenadrine.

3. Isolated Frog Rectus Abdominis Muscle

Orphenadrine showed antagonism to acetylcholine-induced contractions of the rectus muscle. Following 25 µg. per ml. of orphenadrine, the magnitude of the acetylcholine-induced contractions was reduced from 50 to 70%. Maximum block was often seen during the next addition of acetylcholine following wash out of orphenadrine. Recovery of the muscle from the orphenadrine-induced block took a considerable time in spite of repeated washings (Fig. 69). There appears to be an additive effect between the neuromuscular block induced by tubocurarine and that induced by orphenadrine. Thus in one preparation (Fig. 70) orphenadrine 25 µg. per ml. produced about 80% block while tubocurarine 2 ug. per ml. produced about 50% block. Both drugs given together in the same doses produced complete neuromuscular block.

4. Isolated Rat - Phrenic Nerve Diaphragm Preparation

Orphenadrine in a dose range of 1.0 µg. to 6.0 µg. per ml. reduced the diaphragm twitch height following indirect stimulation via the phrenic nerve. Altogether eleven preparations were made and the sensitivity to orphenadrine was found to vary somewat from preparation to preparation. Tubocurarine was from 8 to 15 times more potent than orphenadrine. /

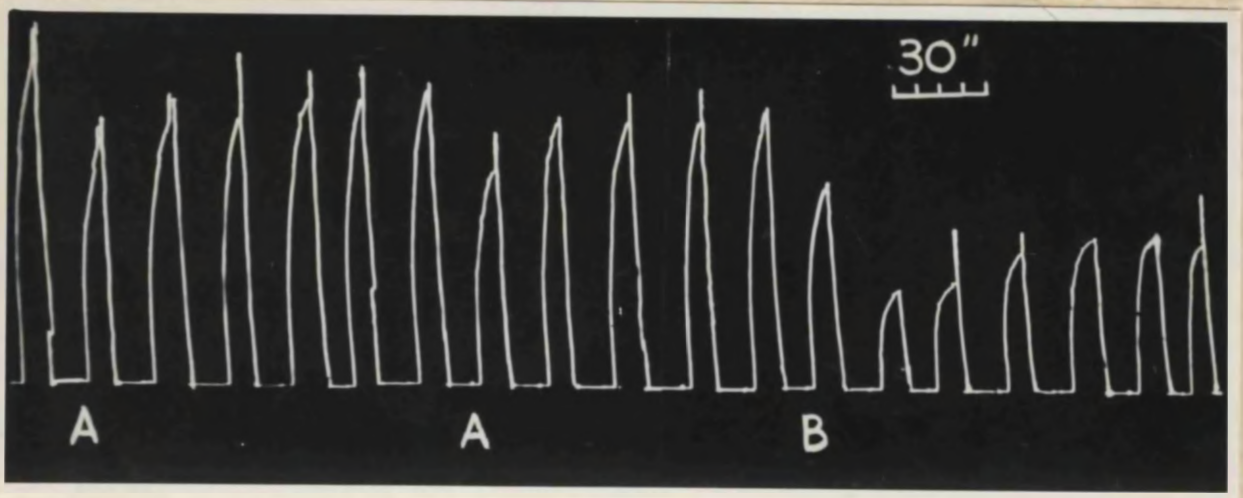


Fig. 69. Isolated frog rectus abdominis muscle. All contractions were due to 3 µg. per ml. acetylcholine acting for 45 seconds. Labelled contractions were preceded 15 seconds earlier by

At A, tubocurarine 2 µg. per ml.

At B, orphenadrine, 25 µg. per ml.

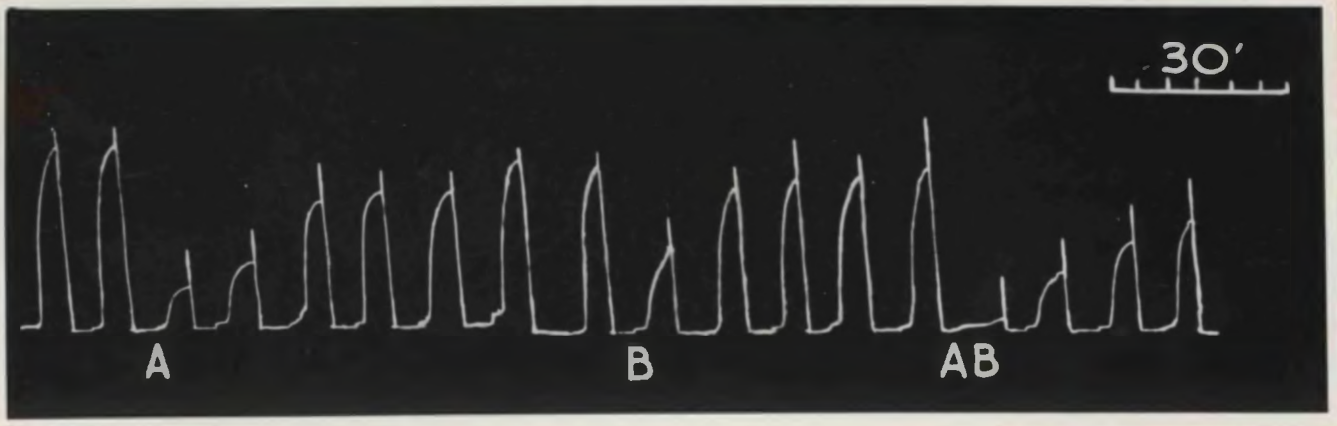


Fig. 70. Isolated frog rectus abdominis muscle. All contractions were due to 3 µg. per ml. of acetylcholine acting for 45 seconds. Labelled contractions were preceded 15 seconds earlier by

At A, orphenadrine 25 µg. per ml.

At B, tubocurarine 2 µg. per ml.

At AB, orphenadrine 25 µg. per ml. and tubocurarine 2 µg. per ml.

orphenadrine. When complete block was induced by orphenadrine, the response to direct stimulation showed that the muscle was not primarily affected (Fig. 71). The neuromuscular block induced by a constant dose of orphenadrine sometimes increased with each subsequent addition of the drug. Thus orphenadrine 25 µg. per ml. produced no reduction in the twitch height after acting for a period of three minutes. The bath was washed out and orphenadrine was again added to the bath to produce a concentration of 25 µg. per ml. This time an approximately 35% reduction in twitch height was produced. The bath was again washed out and when contractions had returned to the initial height orphenadrine was added to the bath to give the same concentration as before. A nearly complete neuromuscular block was then produced in three minutes. The block became complete in spite of the fact that the bath was washed out three times (Fig. 73). Recovery after a block by orphenadrine, in spite of repeated washing, usually took a long time on the average about three times as long as after the same degree of neuromuscular block produced by tubocurarine. Sometimes even after 60 to 80 minutes and after repeated washing, the twitch height had only recovered to about 60 to 70 per cent of the initial height. This finding indicates that orphenadrine is more strongly bound to the receptors at the neuromuscular synapse than tubocurarine.

"UK. 738", 10 µg. per ml. was found not to have any significant effect on the twitch height. Ethopropazine on the other hand in a dose of 25 µg. per ml. behaved like orphenadrine although the neuro-

muscular /

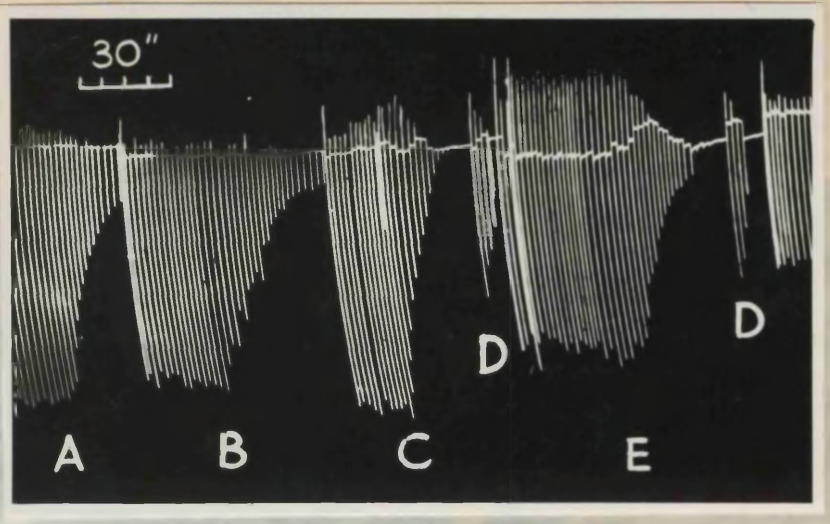


Fig. 71. Isolated rat phrenic nerve-diaphragm preparation. Contractions induced by indirect stimulation via the phrenic nerve or by direct stimulation of the muscle - "D".
At A, tubocurarine 4 µg. per ml.
At B, " 6 µg. per ml.
At C, " 8 µg. per ml.
At E, orphenadrine 50 µg. per ml.

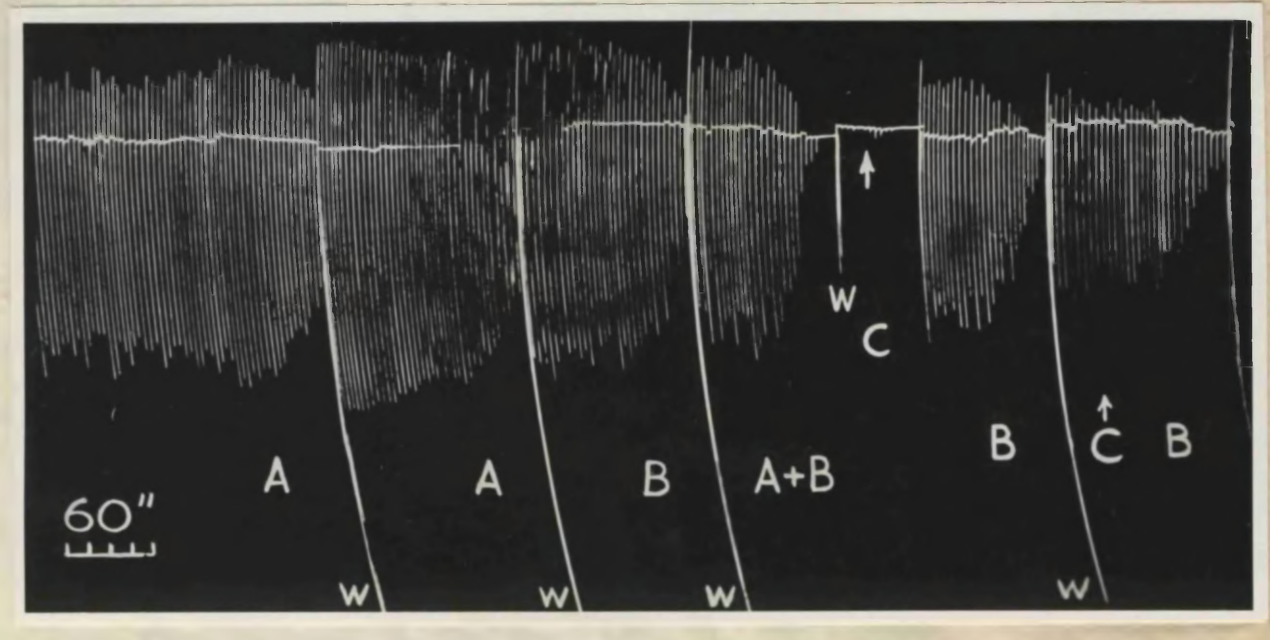


Fig. 72. Isolated rat phrenic nerve-diaphragm preparation. Contractions induced by indirect stimulation via the phrenic nerve. W = Wash out.
At A, ethopropazine 25 µg. per ml.
At B, orphenadrine 12.5 µg. per ml.
At C, neostigmine 25 µg. per ml.

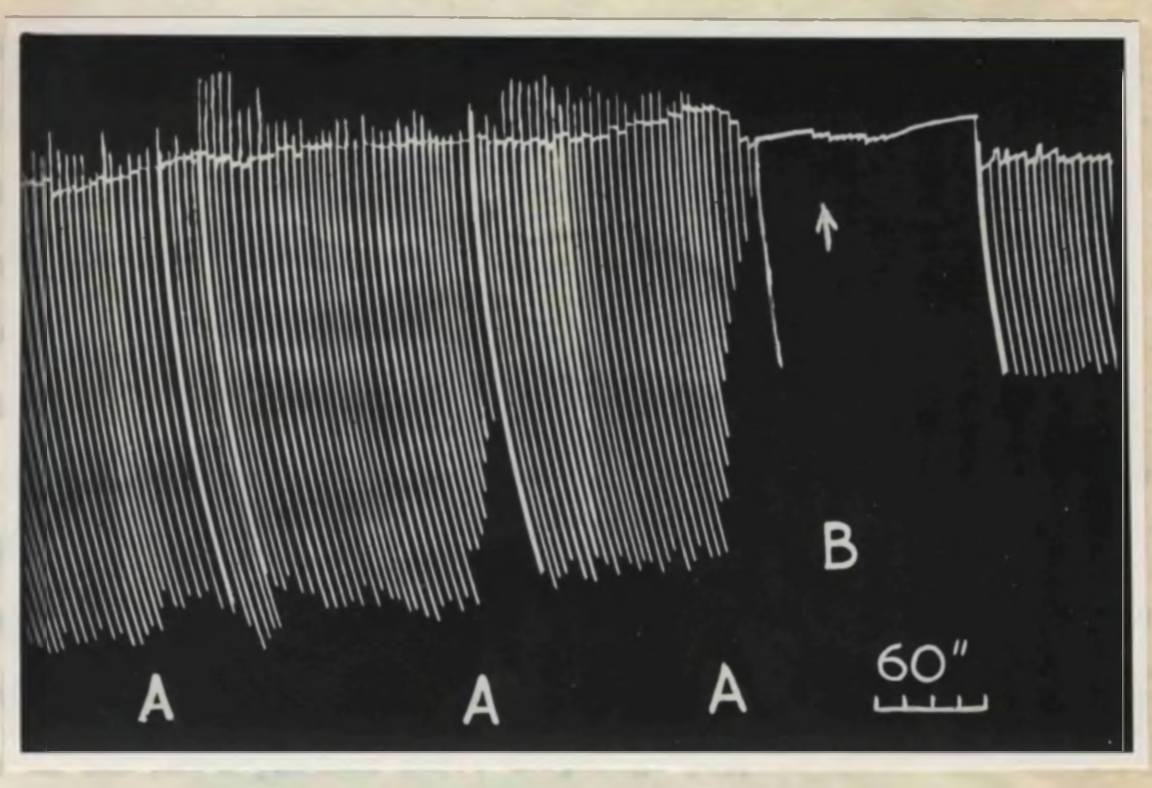


Fig. 73. Isolated rat phrenic nerve-diaphragm preparation. Indirect stimulation via the phrenic nerve.

At A, Orphenadrine 25 µg. per ml.
At B, Edrophonium 5 µg. per ml.

neuromuscular blocking action appears to be weaker than that of orphenadrine. There appeared to be some additive effect between the block induced by orphenadrine and that induced by ethopropazine (Fig. 72).

Neostigmine (Prostigmin) 2.5 µg. to 25 µg. per ml. did not significantly affect complete neuromuscular block induced by orphenadrine. Edrophonium ("Tensilon") 5 µg. per ml. also had no significant effect on complete neuromuscular block induced by orphenadrine. although in this dose it antagonised a partial block induced by orphenadrine. There was an additive effect between the block induced by tubocurarine and that caused by orphenadrine (Fig. 74). It would appear from the two preparations on which this was tested that there was no antagonism between the blocks induced respectively by suxamethonium and orphenadrine on the rat's phrenic nerve-diaphragm preparation. In fact, orphenadrine had a potentiating effect on the neuromuscular block caused by suxamethonium. Thus in one preparation suxamethonium 5 µg. per ml. produced approximately a 40 per cent block. Orphenadrine 12.5 µg. had no neuromuscular blocking effect but this dose of orphenadrine acting simultaneously with suxamethonium at the previous dose level produced approximately 93 per cent neuromuscular block (Fig.76).

5. Effects of Orphenadrine on Spinal Reflexes

(a) Knee jerks. 5 cats were used for this study. Orphenadrine 1.0 mg. per kg. had no effect on the knee jerk. On the other hand, 3.0 mg. per kg. had no effect on the reflex in 2 cats, caused depression /

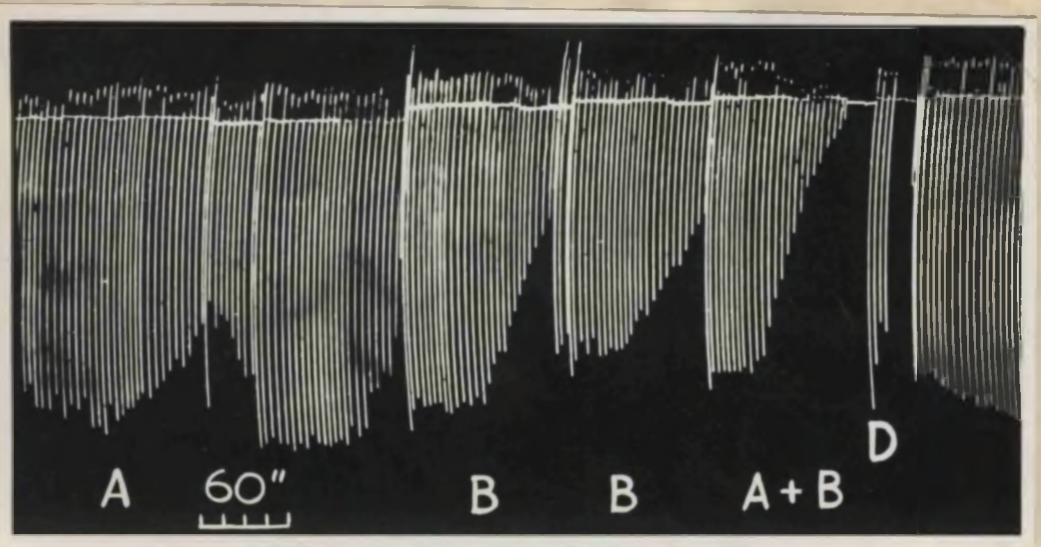


Fig. 74. Isolated rat phrenic nerve-diaphragm preparation. Indirect stimulation via the phrenic nerve. At D direct stimulation of the muscle.
At A, orphenadrine 25 µg. per ml.
At B, tubocurarine 2 µg. per ml.

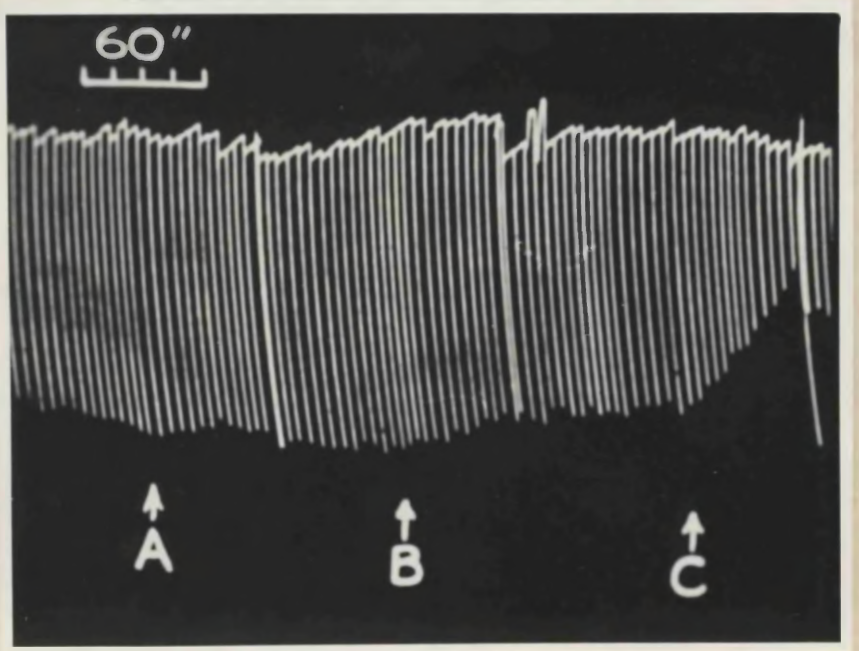


Fig. 75. Isolated rat phrenic nerve-diaphragm preparation. Indirect stimulation via the phrenic nerve.
At A, UK. 738 5 µg. per ml.
At B, UK. 738 10 µg. per ml.
At C, orphenadrine 10 µg. per ml.

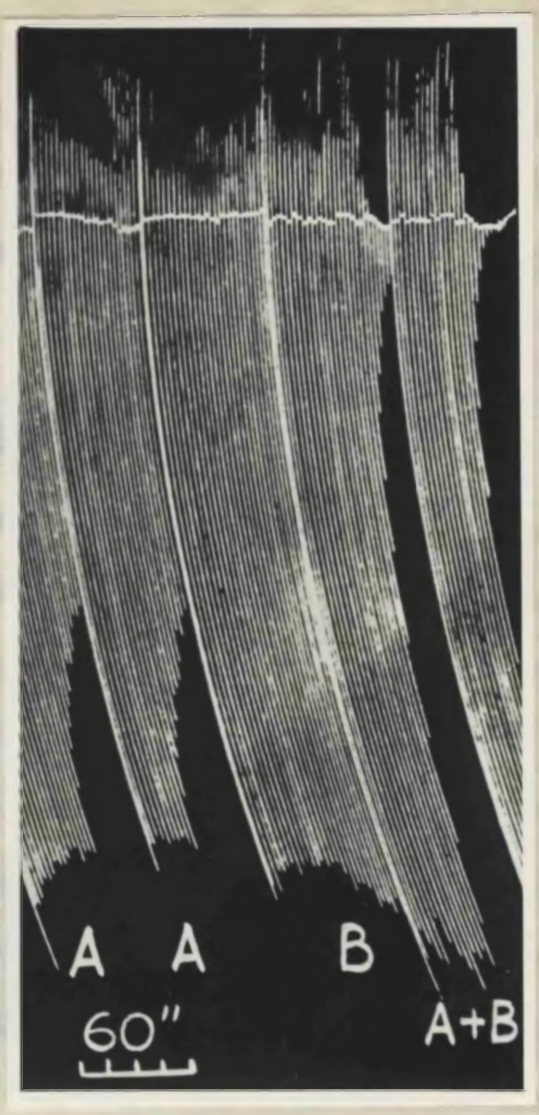


Fig. 76. Isolated rat phrenic nerve-diaphragm preparation. Indirect stimulation via the phrenic nerve.

At A, suxamethonium 5 µg. per ml.

At B, orphenadrine 12.5 µg. per ml.

depression in one cat and an increase in the size of the reflex response in 2 cats. With regard to 5 mg. per kg. there was no effect in 2 cats, depression in 2 cats and in one of them there was complete depression of the reflex after 15 minutes (Fig. 77). In this cat the depression was preceded by a short-lived increase in the size of the reflex response.

(b) Crossed Extensor Reflex

Another 6 cats were used in this study. At a dose level of 3.0 mg. per kg., orphenadrine produced no effect in 2 cats, increased the size of the reflex response in another 2 cats and in the remaining 2 cats the size of the reflex response was depressed. In the dose level of 5.0 mg. per kg., orphenadrine produced depression of the reflex in 3 out of the 6 cats, no effect in 2 cats and increase in the reflex response in one cat. It must be mentioned that in one of the cats which showed depression of the reflex, depression was preceded by an increase in the size of the response. One feature of the effect of orphenadrine in spinal cats is the production of muscle spasms which usually starts within one minute of the injection although in one of the 4 cats which showed this phenomenon, it was delayed for 20 minutes after injection of orphenadrine. The spasms are usually short-lived, lasting only about one minute, but lasted for up to twenty minutes in one instance. When the spasms occurred immediately after the injection of orphenadrine, they were associated with an immediate increase in the size /

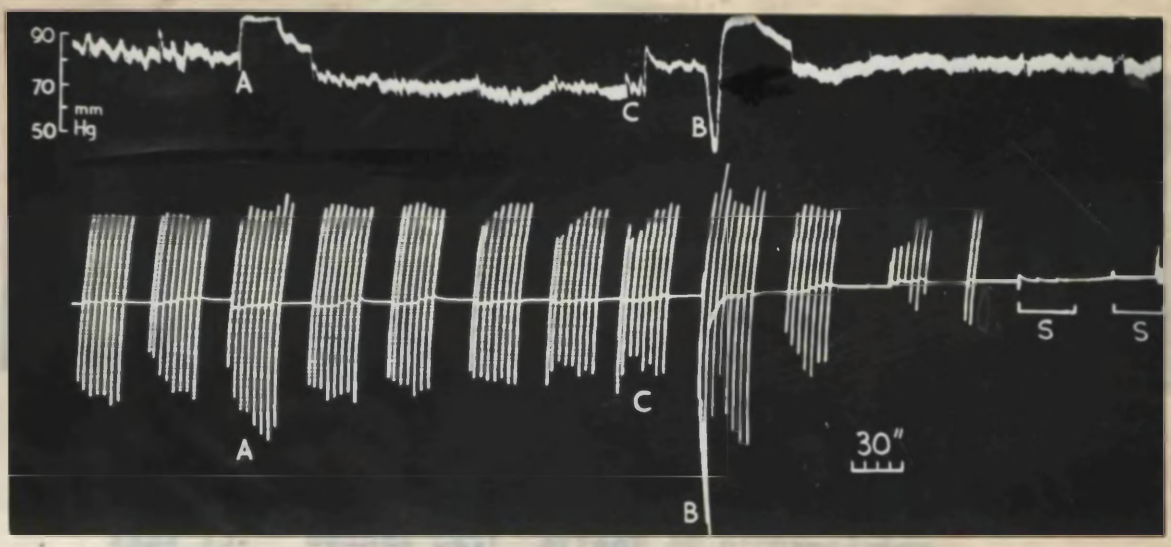


Fig. 77. Spinal Cat: Effect of orphenadrine on the knee jerk.
Lower record - Knee jerks elicited for 2 minutes every 5 minutes.
Upper record - Blood pressure.
At A, orphenadrine 3 mg. per kg.
At B, orphenadrine, 5 mg. per kg.
At C, normal saline 8 ml.
S patellar stimulated.

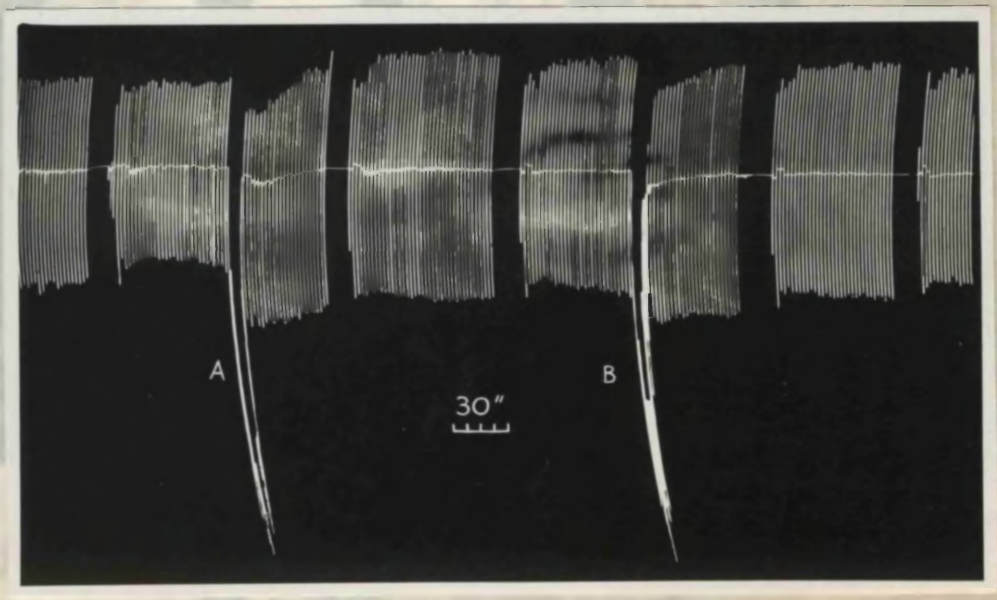


Fig. 78. Spinal Cat: Effect of orphenadrine on the crossed extensor reflex.
At A, orphenadrine 3 mg. per kg.
At B, orphenadrine 5 mg. per kg.

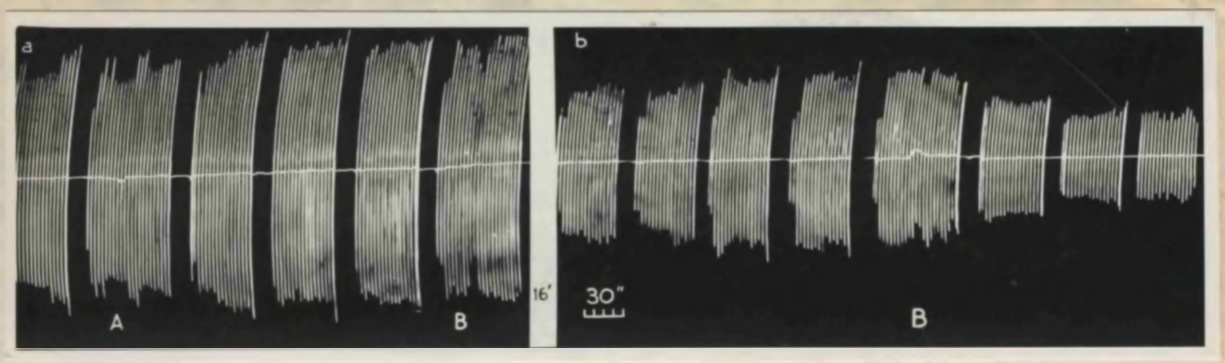


Fig. 79. Spinal Cat: Effect of orphenadrine on the crossed extensor reflex.

At A, orphenadrine 3 mg. per kg.
At B, orphenadrine 5 mg. per kg.

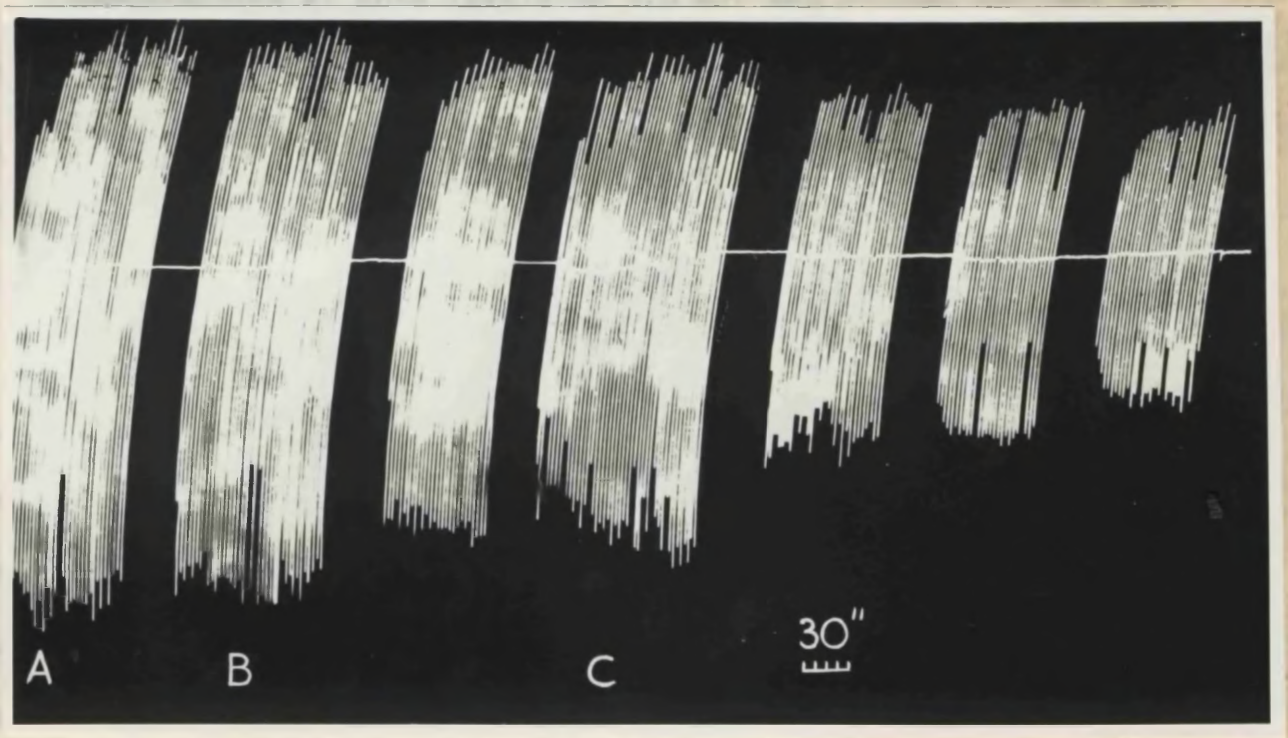


Fig. 80. Spinal Cat: Effect of orphenadrine on the crossed extensor reflex.

At A, orphenadrine 1 mg. per kg.
At B, orphenadrine 3 mg. per kg.
At C, orphenadrine 5 mg. per kg.

size of the reflex response (Fig. 78). Five mg. per kg. was more potent than 3.0 mg. per kg. in producing muscular spasm. In some cats, orphenadrine may therefore have an initial excitatory phase in its action which is characterised by muscle spasm and an increase in the size of the spinal reflex responses. This excitatory phase is short-lived and may be followed by a phase of depression in which the size of the reflex response is diminished and may in fact be completely abolished.

6. Blood Pressure of the Anaesthetised Cat

Orphenadrine at dose levels of 3.0 mg. and 5.0 mg. per kg. produced a sharp fall in the blood pressure which usually returned to its original level (and in some cases reached a higher level) within one or two minutes (Figs. 81 and 82). The fall in blood pressure was proportional to the dose given.

The pressor effects of adrenaline and noradrenaline were not affected by pretreatment with orphenadrine but the time taken for the blood pressure to return to its original level after it had been raised by adrenaline or noradrenaline was very significantly shortened by injecting orphenadrine 3.0 mg. per kg. at the height of the pressor effect (Fig. 81).

7. Blood Pressure of the Spinal Cat

Orphenadrine at dose levels of 3.0 mg. or 5.0 mg. per kg. produced

a /

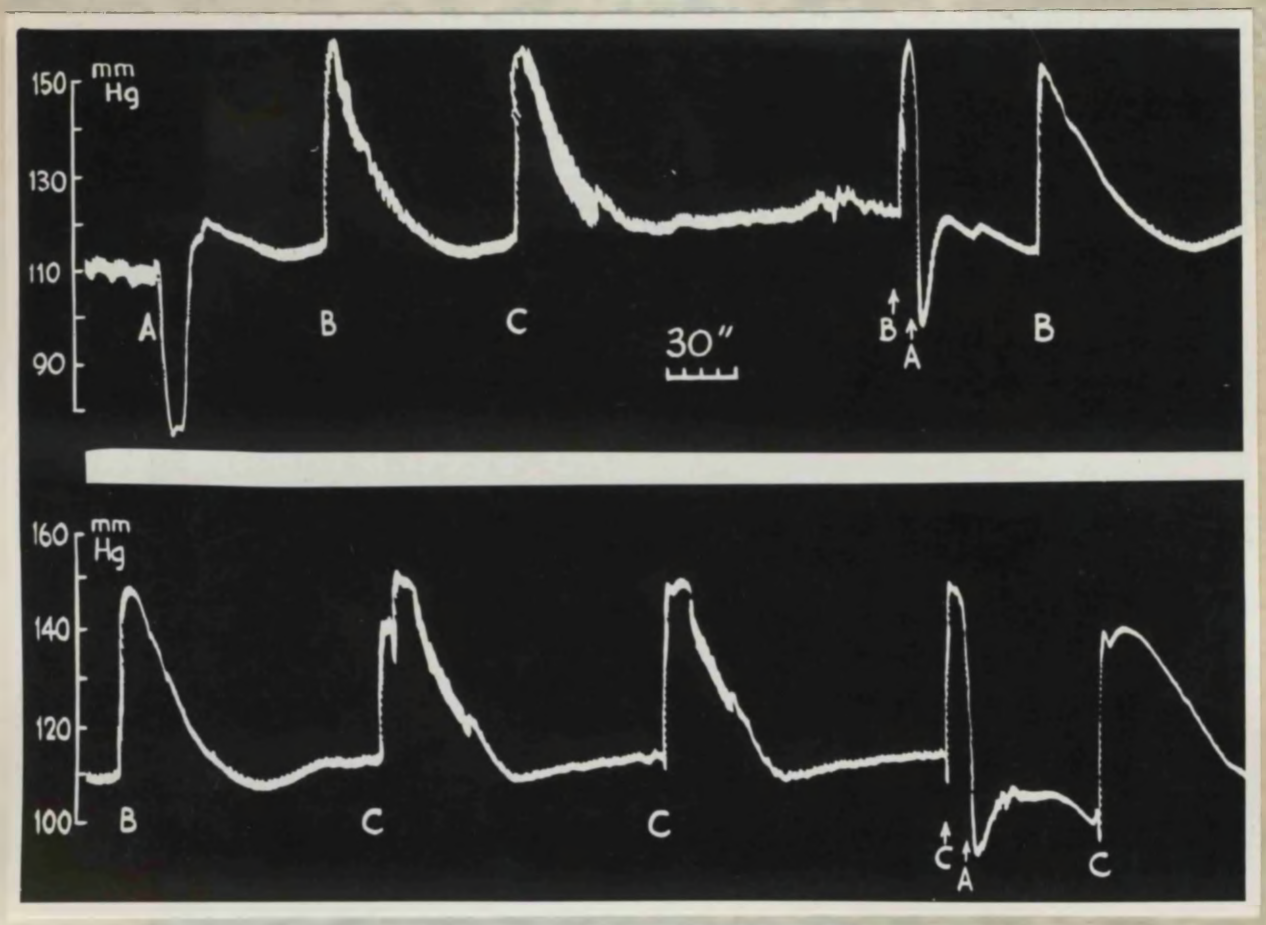


Fig. 81. Cat: Pentobarbitone anaesthesia. Effect of orphenadrine on the blood pressure. Blood pressure record from the common carotid artery. Drugs administered intravenously.

At A, orphenadrine 3 mg. per kg.
At B, adrenaline 8 µg.
At C, noradrenaline 8 µg.

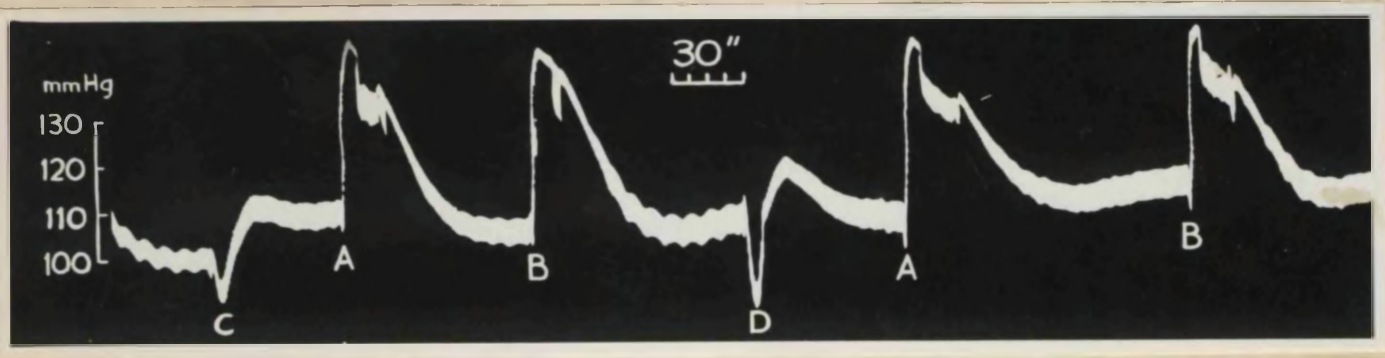


Fig. 82. Cat: Pentobarbitone anaesthesia. Effect of orphenadrine on the blood pressure. Blood pressure record from the common carotid artery. Drugs administered intravenously.

At C, orphenadrine 3 mg. per kg.
At A, adrenaline 4 µg.
At B, noradrenaline 4 µg.
At D, orphenadrine 5 mg. per kg.

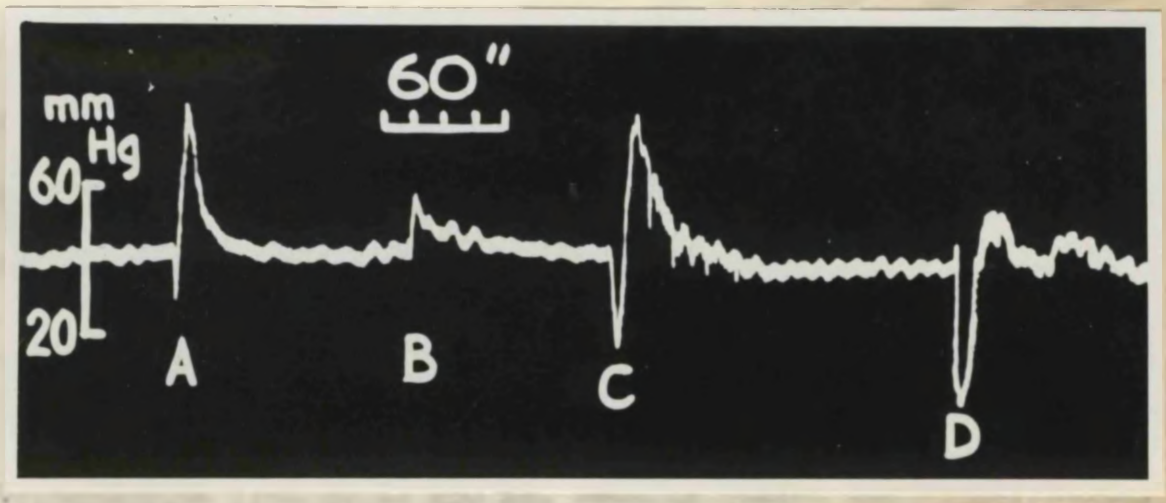


Fig. 83. Spinal Cat. Effect of orphenadrine on the blood pressure. Blood pressure record from the common carotid artery. Drugs administered intravenously.

At A, orphenadrine, 1 mg. per kg.
At B, normal saline 3 ml.
At C, orphenadrine, 3 mg. per kg.
At D, orphenadrine, 5 mg. per kg.

a sharp fall in the blood pressure level, which returned to its original value (and in some cases reached a higher level) within one or two minutes. The fall in blood pressure was proportional to the dose given (Fig. 83).

8. Nictitating Membrane of the Anaesthetised Cat

Orphenadrine in doses of 3.0 mg. and 5.0 mg. per kg. showed no direct effects upon the nictitating membrane of the anaesthetised cat. It also caused no significant depression in the magnitude of contractions following tetanisation of the cervical sympathetic. Ethopropazine 5.0 mg. per kg. (in 2 out of 3 cats) had a somewhat greater depressant effect on the contractions due to tetanisation of the cervical sympathetic. This depressant effect on the cervical sympathetic was very much less than that due to hexamethonium 1.5 to 2.0 mg. per kg. (Fig. 84), although the fall in blood pressure was much more marked with 5.0 mg. per kg. of ethopropazine.

9. Isolated Perfused Rat Hindquarters

Orphenadrine from 50 to 250 µg. usually caused vasoconstriction, but in several experiments 50 µg. had no effect on the vasomotor tone. The degree of vasoconstriction was proportional to the dose of orphenadrine given (Fig. 85). There was an additive effect between the vasoconstrictor action of adrenaline and noradrenaline and that of orphenadrine (Figs. 85, 86 and 87). Pretreatment with tolazoline did not /

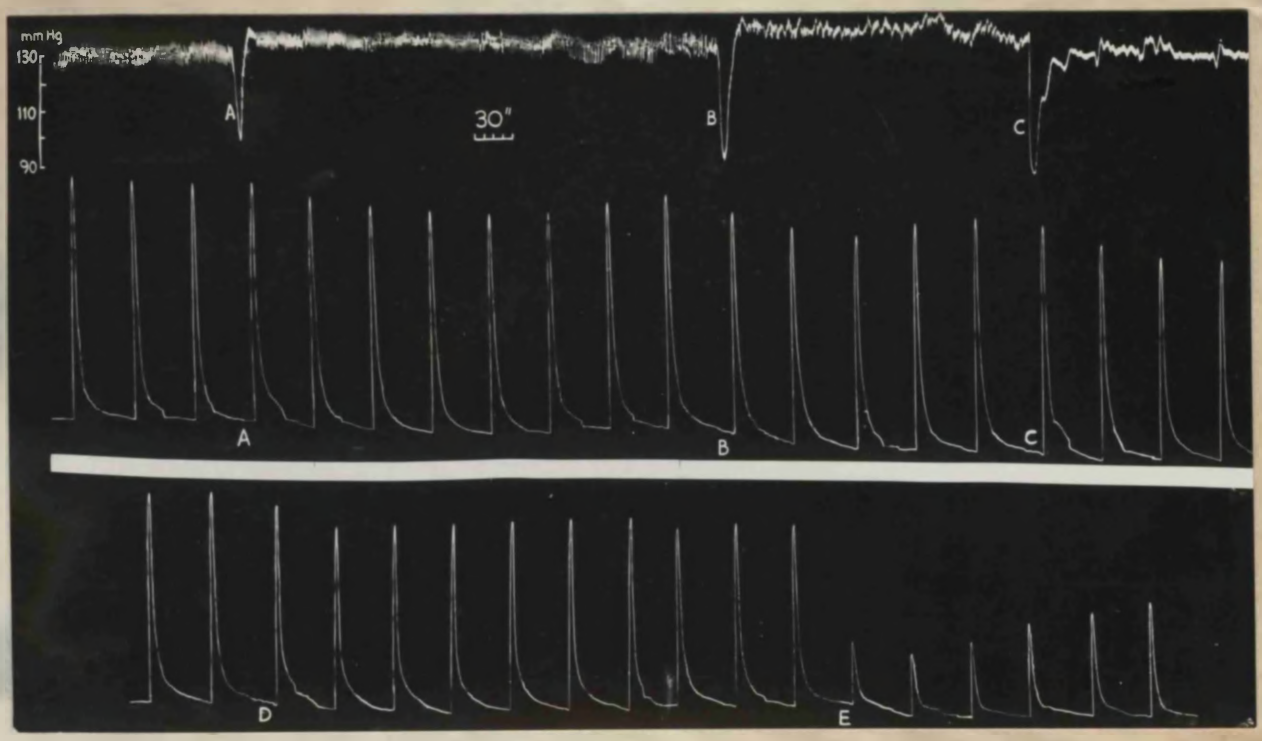


Fig. 84. Cat. Pentobarbitone anaesthesia. Contractions of nictitating membrane elicited at intervals of three minutes by preganglionic stimulation at a frequency of 1,200 impulses per minute, 20 volts amplitude and pulse width of 1.5m.sec. for 5 seconds.

The uppermost tracing is a record of the blood pressure from a common carotid artery.

At A, orphenadrine, 3 mg. per kg.
At B, orphenadrine, 5 mg. per kg.
At C, ethopropazine 3 mg. per kg.
At D, ethopropazine 5 mg. per kg.
At E, hexamethonium 2 mg. per kg.

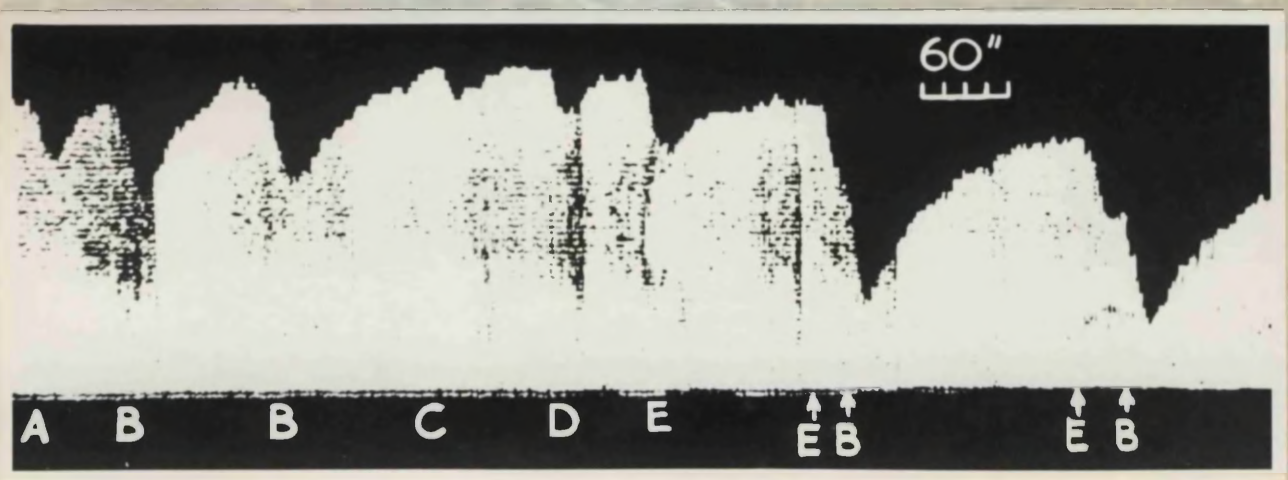


Fig. 85. Perfusion of isolated rat hindquarters; depressions indicate vasoconstriction.

At A, noradrenaline 2 µg.
At B, noradrenaline 3 µg.
At C, orphenadrine 50 µg.
At D, orphenadrine, 125 µg.
At E, orphenadrine, 250 µg.

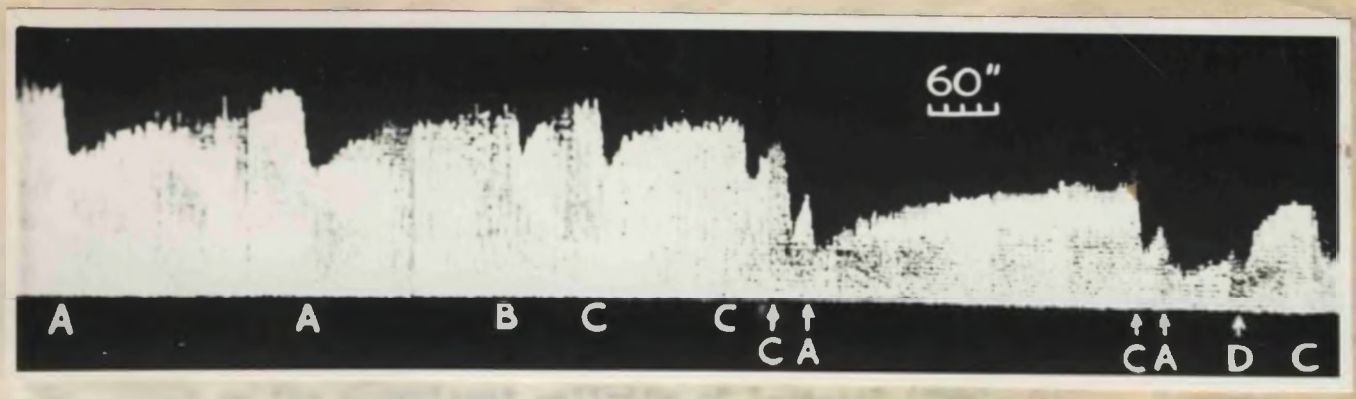


Fig. 86. Perfusion of isolated rat hindquarters. Depressions indicate vasoconstriction.

At A, noradrenaline 2 µg.
At B, orphenadrine 50 µg.
At C, orphenadrine 125 µg.
At D, tolazoline 5 mg.

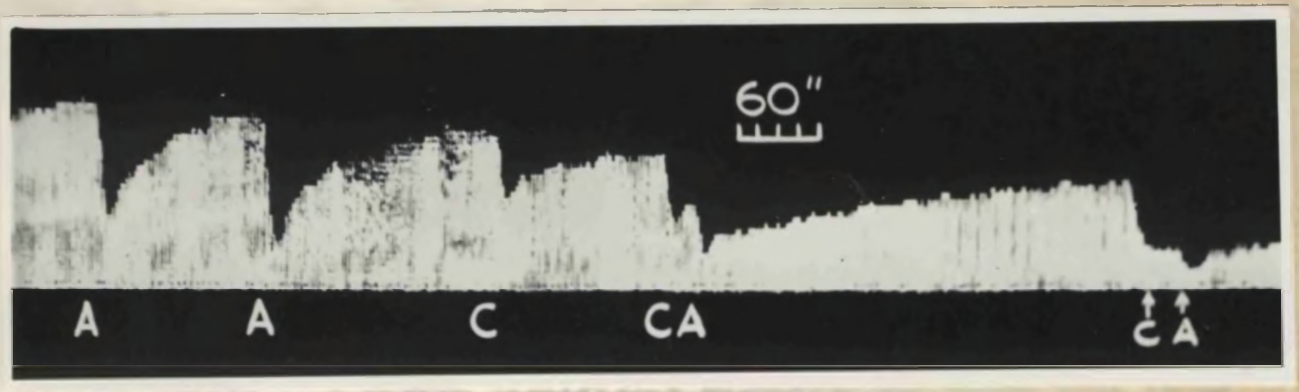


Fig. 87. Perfusion of isolated rat hindquarters. Depressions indicate vasoconstriction.

At A, adrenaline 5 µg.
At B, orphenadrine 125 µg.

not prevent the vasoconstrictor action of orphenadrine (Fig. 86).

10. The Effect of Orphenadrine on the Convulsant Activity of Leptazol

Orphenadrine at dose levels of 1 mg., 3 mg., and 15 mg. per kg. had no effect on the convulsant activity of leptazol (Table 25). However, at a dose level of 15 mg. per kg. there was a significant reduction in mortality due to leptazol. Thus the mortality due to 40 mg. per kg. of leptazol was reduced from 50 per cent to 0 per cent and the mortality due to 60 mg. per kg. of leptazol was reduced from 60 per cent to 20 per cent (Table 26). In contrast, 1 mg. and 3 mg. per kg. of orphenadrine had no effect on the mortality due to leptazol.

11. The effect of Orphenadrine on Electroshock Seizures

Orphenadrine at a dose level of 3 mg. and 6 mg. per kg. had no effect on the incidence of electroshock seizures. At a dose level of 12 mg. per kg. there was some reduction in the incidence of electroshock seizures. A highly significant reduction was noted with 15 mg. per kg. (Table 27). Thus 6 out of 20 mice showed positive reactions to electroshock before treatment with orphenadrine 1.5 mg. per kg. while no mice showed a positive reaction after this treatment.

Dose of Orphenadrine	Percentage of Animals Convulsing			
	Leptazol 20 mg/Kg.	Leptazol 30 mg/Kg.	Leptazol 40 mg/Kg.	Leptazol 60 mg/Kg.
-	20%	70%	90%	100%
1 mg./Kg.	-	70%	100%	100%
3 mg./Kg.	20%	80%	90%	100%
15 mg./Kg.	-	70%	80%	100%

TABLE 25. Effect of pretreatment with orphenadrine on the convulsant activity of Leptazol.

Dose of Orphenadrine	Percentage of Mortality			
	Leptazol 20 mg/Kg.	Leptazol 30 mg/Kg.	Leptazol 40 mg/Kg.	Leptazol 60 mg/Kg.
-	0%	0%	50%	60%
1 mg./Kg.	0%	0%	50%	70%
3 mg./Kg.	0%	0%	40%	60%
15 mg./Kg.	0%	0%	0%	20%

TABLE 26. Effect of pretreatment with orphenadrine on the mortality due to Leptazol.

Dose of Orphenadrine	No. of positive (out of 20 mice)	
	Before Orphenadrine	After Orphenadrine
3 mg./Kg.	5	5
6 mg./Kg.	7	7
12 mg./Kg.	5	3
15 mg./Kg.	6	0

TABLE 27. Effect of pretreatment with orphenadrine on electro-convulsive seizures.

DISCUSSION

The experiments on the isolated frog rectus muscle and on the rat phrenic nerve-diaphragm preparation demonstrated the neuromuscular blocking activity of orphenadrine. There is an additive effect between the neuromuscular blocking activity of orphenadrine and that of tubocurarine and it may reasonably be concluded that in these two preparations the block produced by orphenadrine is allied to the competitive type. In these two preparations tubocurarine is about 8 to 15 times more potent than orphenadrine.

It would appear that in the cat the neuromuscular blocking potency of orphenadrine is not as great as in the frog or the rat. Thus 150 µg. per kg. of tubocurarine will produce 20 to 50 per cent block in the cat and yet orphenadrine in a dose of 6 mg. per kg. did not produce any visible neuromuscular block. However, the profound antagonism to suxamethonium-induced neuromuscular block and the potentiation of tubocurarine-induced block on the cat's gastrocnemius muscle-sciatic nerve preparation demonstrate the fact that although no reduction in twitch tension accompanies an intravenous dose of 3 mg. to 6 mg. of orphenadrine, profound changes take place at the neuromuscluar synapse which affect the pharmacological activity of the drugs at this site. It is likely that orphenadrine, like tubocurarine, produces its neuromuscular blocking activity by competing with acetylcholine and other depolarising agents for the end plate receptors to which these compounds become /

become attached or with which they react.

In the hen the action of orphenadrine at the neuromuscular junction is difficult to assess. Orphenadrine can produce a mild degree of neuromuscular block at a dose level of 3.0 mg. per kg. and it potentiats the block induced by tubocurarine. Its action on the effects of suxamethonium is complicated. Thus orphenadrine is capable of reducing the degree of contracture induced by suxamethonium but in a majority of cases it prolongs the neuromuscular blocking activity of this drug.

Suxamethonium and decamethonium (C_{10}) are generally accepted as typical depolarising drugs, but it is now known that this is only true for certain animal species. Zaimis (1952 and 1953) showed that in monkeys, dogs, rabbits and the hare, decamethonium behaves like a competitive neuromuscular blocking agent. Hall and Parkes (1953) showed that the neuromuscular block induced by decamethonium and suxamethonium in guinea pigs was of the competitive variety. Churchill-Davidson and Richardson (1952 and 1953) demonstrated that in patients suffering from myasthenia gravis, decamethonium behaved as a competitive neuromuscular blocking agent. In birds, suxamethonium when injected intravenously produced contracture and a decrease in the amplitude of the height of the muscle contractions. Crema, Scognamiglio and Bovet (1959) showed that these two phenomena of contracture and neuromuscular block were relatively independent of each other. They found that tubocurarine antagonised decamethonium with regard to the contracture, whilst their blocking /

blocking activities were additive. They suggested that in birds the contracture was due to depolarisation but the neuromuscular block was of the competitive variety.

As already stated, the results of the experiments reported in this chapter show that orphenadrine can prolong the neuromuscular block induced by suxamethonium, an action not unlike that reported for tubocurarine by Crema and his colleagues. Further, after pretreatment with orphenadrine, the block induced by suxamethonium is antagonised by neostigmine - indicating that the block is now of the competitive type. It is reasonable, therefore, to conclude that in the hen orphenadrine also behaves like a competitive neuromuscular blocking agent. Orphenadrine probably changes the nature of the membrane at the neuromuscular synapse and thus changes the nature of the block caused by a typical depolarising drug to a competitive type. This is analagous to the state in man where, as Zaimis (1953) suggested, a change occurs at the muscle membrane of the neuromuscular junction in patients suffering from myasthenia gravis causing a transformation of the pure depolarisation caused by decamethonium into a true competitive block.

In rats, complete agreement has not been reached on the mode of action of suxamethonium and decamethonium on the neuromuscular synapse but Jarcho and his colleagues (1950 and 1951) have shown that in the innervated muscle of the rat, a partial neuromuscular block induced by tubocurarine could be completed by decamethonium. They also found that both tubocurarine and decamethonium caused a reduction in end-

. plate /

plate potential in the innervated muscle of the rat. The results in the rat are in contrast to those obtained in the cat. In this species decamethonium produces a depolarising block and tubocurarine, a competitive block; each drug antagonising the neuromuscular blocking activity of the other (Paton, 1951). It would appear therefore that in rats decamethonium and suxamethonium behave at least in part, as competitive neuromuscular blocking agents. This explains the findings in the present study that in the rat phrenic nerve diaphragm preparation orphenadrine and tubocurarine potentiated the neuromuscular blocking activity of suxamethonium.

In the rat phrenic nerve diaphragm preparation, it was found that the neuromuscular blocking activity of orphenadrine lasted longer than that caused by tubocurarine in equipotent doses. A similar effect was also seen in the isolated frog rectus preparation. In the rat phrenic nerve diaphragm preparation, it was also found that subsequent additions of orphenadrine, after the muscle had apparently recovered from the effect of the previous dose, tended to increase the degree of neuromuscular block. Thus in one preparation orphenadrine 25 µg. per ml. produced no neuromuscular block on the first addition, but on the third addition produced complete neuromuscular block (Fig. 73, p. 321).

It is reasonable to conclude that although the neuromuscular blocking activity of tubocurarine may be more than ten times that of orphenadrine, the effect of the latter on the neuromuscular synapse lasts much longer. In the cat gastrocnemius sciatic nerve preparation /

preparation the effect of orphenadrine on the neuromuscular synapse (as judged by its antagonism to the neuromuscular block induced by suxamethonium lasts for about one hour.

The effects of orphenadrine on the convulsant activity and mortality due to leptazol, and on electroshock seizures are of great interest. As already stated, orphenadrine even in rather high doses (15 mg. per kg.) had no effect on the convulsant activity of leptazol. This is in contrast to the results of Cronheim (1958) who found that orphenadrine lowered the threshold of leptazol-induced convulsions. It must be mentioned, however, that it was observed that the mouse became more agitated in the first minute or two after injecting 15 mg. per kg. of orphenadrine intravenously. Two out of 52 mice given this dose of orphenadrine died from convulsions within the first two minutes of the injection. It appears therefore, that orphenadrine at this dose level may have an initial excitatory phase soon followed by a depressant action. Thus it is conceivable that if leptazol was injected within two minutes of injecting orphenadrine, there might have been an increase in the convulsant activity of leptazol, in other words a lowering of the threshold of the convulsant action of leptazol. Cronheim, however, did not state the time relationship between the administration of both drugs.

Of greater interest is the fact that orphenadrine at a dose level of 15 mg. per kg. significantly reduced the susceptibility of mice to electroshock seizures and also significantly decreased the mortality

from /

from leptazol. It was noted that the mice which died from leptazol were from among those that showed full extension of the hind limbs during the later phase of the leptazol-induced convulsions. It was noted also that although orphenadrine at a dose of 15 mg. per kg. did not affect the clonic phase of leptazole-induced convulsions, it reduced the tonic phase, i.e., the full extension of the hind limbs. It is difficult to explain this action of orphenadrine at this dose level but Goodman, Grewal, Brown and Swinyard (1953) in a study of the modification of maximal seizures induced by leptazol and electroshock in mice by anticonvulsants, made the point that the initial clonus of leptazol-induced seizures is probably due to the early selective stimulation of the motor cortex, before the intravenously-injected leptazol had reached a concentration capable of causing the localised areas of high frequency repetitive discharges and the appropriate seizure spread there-from,which is responsible for the production of the tonic seizure (extension of the hind limbs). It is therefore probable that orphenadrine at this dose level (15 mg. per kg.) inhibits seizure spread in the cerebrospinal axis. The site of this inhibition has not been determined in this study but it must not be forgotten that a peripheral skeletal muscle relaxant effect which orphenadrine has been shown to possess may contribute to this anticonvulsant property. The fact that orphenadrine did not reduce the incidence of clonic convulsions can, however, be interpreted according to the hypothesis of Goodman and his colleagues (1953) to mean that the inhibitory effect

is /

is not at the level of cerebral cortex; in other words the inhibition of seizure spread must be at a level below the cerebral cortex.

The relationship between chemical structure and pharmacological activity is very complex and only generalisations (which will necessarily have a number of exceptions) can be made. The neuromuscular blocking activity of tubocurarine, decamethonium and suxamethonium is almost certainly due to the possession of quartenary nitrogen atoms which have certain physio-chemical characteristics in relation to the size of the groups they carry (Barlow and Ing, 1948). Taylor (1951), in a review, made the point that most curariform agents contain nitrogen atoms and these occur as full quartenaries. Compounds containing tertiary nitrogen atoms, however, can be active as neuromuscular blocking agents. If one studies the chemical formulae of orphenadrine or ethopropazine, it will be seen that a tertiary nitrogen atom is present in the side chain. It is possible, therefore, that the neuromuscular blocking activity is due to this tertiary nitrogen atom. It may be that the neuromuscular blocking activity of orphenadrine or ethopropazine can be increased by converting the nitrogen atom into a fully ionised quartenary. It must be mentioned, however, that in view of the fact that orphenadrine and ethopropazine are not straight chain compounds, but contain benzene rings, the effect of quarternising the nitrogen in the side chain cannot be easily forecast (Muir, 1961; personal communication). "UK. 738" and benzhexol do not contain this tertiary nitrogen atom and do not have any significant neuromuscular /

neuromuscular blocking activity. The activity of atropine and hyoscine resides in the tropic acid moiety which does not contain any nitrogen atom. The bases - tropine and scopine - although containing nitrogen atoms, are relatively inactive pharmacologically (Goodman and Gilman, 1958). Atropine and hyoscine do not therefore have any neuromuscular blocking activity unless given in very high doses. On the other hand oxyphenonium and methantheline which have a quarternary nitrogen possess neuromuscular blocking activity when given in moderate doses (Goodman and Gilman, 1958).

One interesting point emerges from this study - the possible clinical use of orphenadrine to counteract the side-effects of suxamethonium. Suxamethonium is now frequently used as a muscle relaxant in surgical practice and to prevent fractures during electroconvulsive treatment (Thesleff, 1952; Holt, McCandless, Yacoubain and Mebed, 1953; Murray, 1953). One of the chief disadvantages of suxamethonium is the incidence of severe muscular pain occurring from about 8 to 24 hours after its administration and lasting for up to six days (Churchill-Davidson, 1954; Leatherdale, Mayhew and Williams, 1959; Pearcy and Pick, 1960; Foster, 1960). The incidence varies from 6 to 66 per cent in different published series. Up till the present, no adequate treatment has been found for this very incapacitating side-effect. It has been suggested by Morris and Dunn (1957) that 5 mg. of tubocurarine or 40 mg. of gallamine should be given prior to the administration of succinylcholine in order to reduce the incidence of pain. /

pain. This has not been received with much enthusiasm as both drugs have significant neuromuscular blocking actions of their own. In view of the marked antagonistic effect of orphenadrine on suxamethonium -induced block clinical trial of orphenadrine in these patients might be worth while. It is suggested that 100 to 150 mg. by mouth three or four times daily would be a suitable dose and clearly should be started as soon as possible after the operation or electroconvulsive therapy. Presumably premedication with orphenadrine would be inadvisable as this is likely to increase the requirement of suxamethonium. Furthermore, it has been shown that the intensity of muscular twitching and fasciculation occurring with suxamethonium before the onset of paralysis has no significant effect on the incidence of post-suxamethonium muscular pain (Leatherdale, Mayhew and Williams, 1959).

Hitherto no satisfactory antidote to the neuromuscular block caused by suxamethonium has been found. In some cases the prolonged or complete neuromuscular block has been found to be due to the "dual" blockade of suxamethonium in which case the block is of the competitive type. Such neuromuscular block therefore responds to treatment with neostigmine with or without atropine (Bullough, 1957).

In other cases, the complete prolonged neuromuscular block associated with prolonged apnoea is due either to inadvertent overdosage or to a low serum or tissue cholinesterase (Browne, Collier and Somers, 1952; Evans, Gray, Lehman, and Silk, 1952; Stoddart, 1960). In these cases neostigmine is of no value and may even prolong the neuromuscular /

neuromuscular block. The results of the experiments in this study indicate that orphenadrine may be an effective antidote in such cases and a clinical trial is considered to be worthwhile. At present orphenadrine is not available in a preparation suitable for parenteral administration to human subjects. In experimental animals no deleterious effects on the veins were noted when aqueous solutions containing 10 mg. to 20 mg. of orphenadrine per ml. were given intravenously. It is estimated that about 50 to 200 mg. of orphenadrine given intravenously will be adequate in reversing complete neuromuscular block in a normal adult male. Although orphenadrine causes a fall in blood pressure when administered intravenously, this is short-lived and can be substantially prevented by giving adrenaline or adrenaline-like drugs immediately prior to orphenadrine.

Most of the above discussion has been on the incidental findings which may be of use therapeutically. Attention will now be directed to the question of the mode of action of drugs which have been found to be effective in the relief of the rigidity and tremor of Parkinsonism. Most of this discussion will be on the mode of action of orphenadrine and on how rigidity is relieved, as much more is known about the control of muscle tone than about the physiology of tremor. Furthermore, the experimental work described in this section was undertaken with the aim of explaining how orphenadrine relieves rigidity, muscle weakness and easy fatiguability in patients suffering from post-encephalitic Parkinsonism.

In /

In Chapter I (General Introduction) an account was given of how skeletal muscle tone is controlled. The most important conclusions to be drawn from that discussion are:

(1) That the cells of the reticular formation of the brain stem act as supraspinal internuncial neurones to which the basal ganglia, diencephalon, cerebellum and cerebral cortex are connected. In Parkinsonism the facilitatory system of the reticular formation is overactive and this is associated with a great increase in the gamma efferent discharge to the muscle spindles. A drug which depresses the activity of the cells of the reticular formation will therefore abolish the excess gamma efferent discharge and hence hypertonicity of the skeletal muscles.

(2) The reticular formation influences the spinal cord through spinal internuncial cells. Spinal reflex activity is mediated through the internuncial neurones. A drug which depresses the spinal interneurones will also reduce rigidity.

(3) That hypertonia can be abolished by a break in the reflex arc of the servo mechanism responsible for the hypertonia. Thus rigidity can be relieved or abolished by depression of the afferent discharge from the muscle spindles or by depressing the gamma efferent discharge by blockade at the motor end plates of the intrafusal fibres of the muscle spindle. Rigidity can also be abolished by neuromuscular block at the motor end plate in the extrafusal fibres. From this brief resumé it can be readily appreciated that a drug does not necessarily need to have an action on the reticular formation or the basal /

basal ganglia and diencephalon in order to be effective in the treatment of Parkinsonism. Figure 88 indicates the possible sites of action of drugs used for the relief of rigidity in Parkinsonism.

An attempt will now be made to explain the mode of action of orphenadrine in Parkinsonism. Orphenadrine has been shown in this study to have a curare-like action on the motor end plate (of extrafusal fibres) although in cats and therefore probably also in man (Paton, 1951) the neuromuscular block is so weak that in conventional doses there will be no reduction in the power of the muscles; in fact some increase in muscle power may result from such weak neuromuscular blocking activity. This is not infrequently observed in cats with the first dose of tubocurarine of about 50 to 100 μg. per kg. which, instead of producing a reduction in the twitch tension, increases it. This increase in the twitch tension is said to be due to muscular relaxation from weak neuromuscular block. It is therefore reasonable to postulate that one of the ways whereby rigidity is relieved by orphenadrine is by a peripheral tubocurarine-like action at the neuromuscular synapse.

In Parkinsonism and decerebrate rigidity, there is an increase in the gamma efferent discharge to the muscle spindles (Hunt, 1951). It has now been shown that suxamethonium in subparalytic doses increases the afferent discharge from the muscle spindles in the cat (Granit, Skoglund and Thesleff, 1953 a and b). They suggested that this acceleration of spindle afferent discharge is due to a direct action

on /

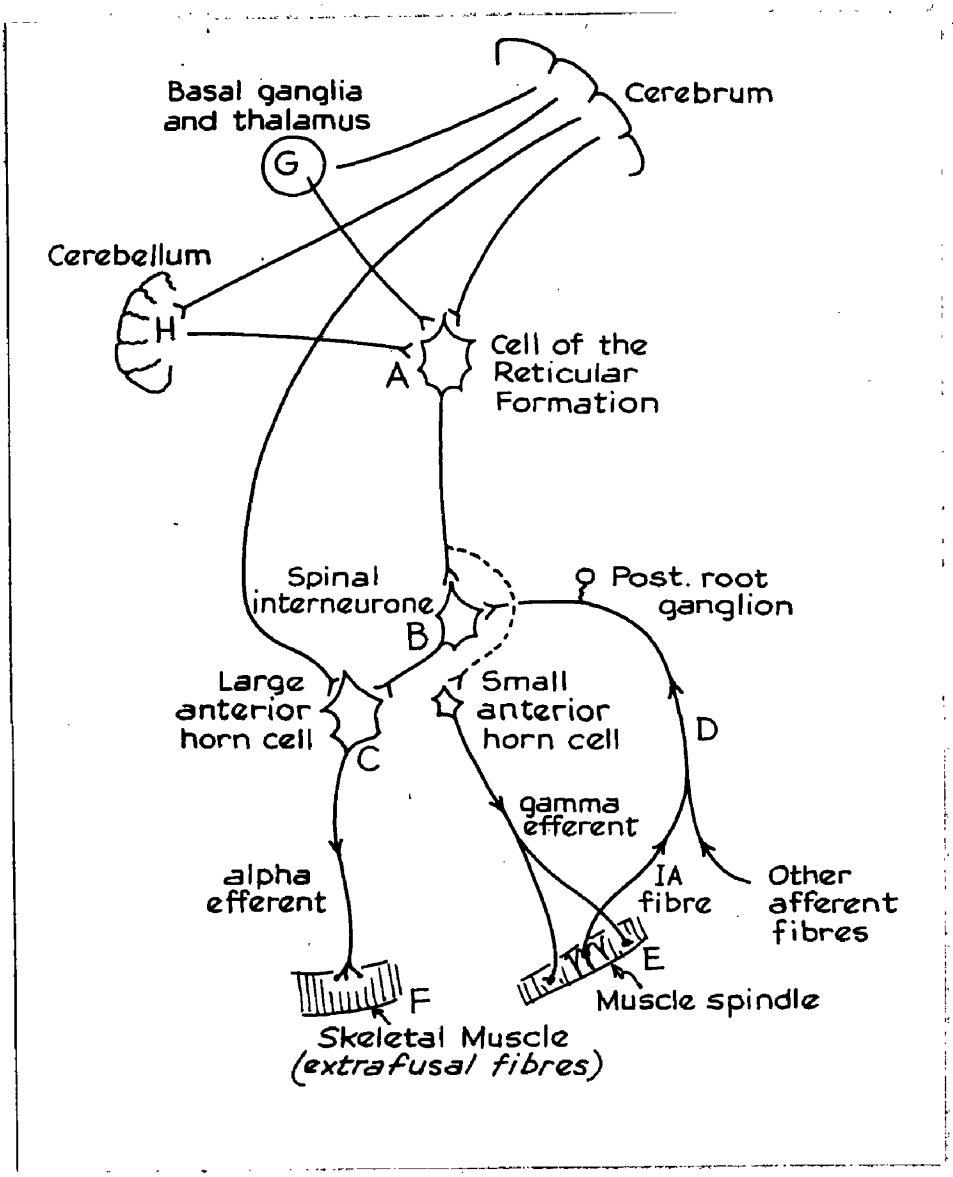


Fig. 88. Diagram showing some of the fibre connections between various structures involved in the pathogenesis of hypertonus in Parkinsonism.

The diagram also indicates the possible sites of action of drugs used for the relief of rigidity in Parkinsonism. The more important sites of action are probably - A, B, E, F and G.

on the sensory endings of the muscle spindle. Smith and Eldred (1961) have, however, shown that this acceleration in the spindle afferent discharge is due to active contraction of the intrafusal fibres of the spindle probably as a result of depolarisation at the end-plate region of the intrafusal fibres. In view of the fact that orphenadrine antagonises the effect of suxamethonium on the motor end plate of the gastrocnemius muscle of the cat, it may well have a depressant effect on the spindle discharge produced by suxamethonium. Further work on this aspect is indicated.

From the above discussion, one can justifiably postulate that orphenadrine can produce skeletal muscular relaxation from purely peripheral mechanisms namely by -

(1) A curare-like action on the synaptic membrane at the neuro-muscular junction.

(2) A possible depressant effect on afferent spindle discharge probably from a depressant action on the motor end plate of the intrafusal fibres of the muscle spindle.

(3) A local anaesthetic effect which has been demonstrated by Bijlsma et al. (1956) may also contribute, although only in a minor way. The effect of a local anaesthetic action of a drug on rigidity has been discussed - Chapter I (page 21).

The effect of orphenadrine on monosynaptic and polysynaptic spinal reflexes is of some interest. Orphenadrine does not have a specific and constant effect on the spinal reflexes. This means that /

that orphenadrine does not rely on a depressant effect on the spinal cord for its skeletal muscle relaxant properties. However the skeletal muscle relaxant action from the peripheral mechanism already described will be enhanced by a depressant action on the spinal cord. On the other hand a stimulant effect on the spinal reflexes may antagonise the peripheral muscle relaxant property. In this context reference should be made to the muscle spasms seen in some of the spinal cats after the administration of orphenadrine. It may be that the myoclonic jerks which were noted as a side-effect of orphenadrine in human subjects are of spinal origin.

The effect of orphenadrine on the reticular formation or the diencephalon has not been investigated in this study. Bijlsma et al. (1956) and De Maar (1956) found that 0.5 to 2.0 mg. per kg. of orphenadrine given intravenously in spinal cats caused no constant changes in the ipsilateral flexor reflex of the cat while in a thalamic cat 0.3 mg. per kg. of orphenadrine injected into the vertebral artery caused a depression of the flexor reflexes. An increase in the reflex was, however, obtained by injecting orphenadrine (1 mg. per kg.) into thalamic cats! They concluded, rather erroneously, that the site of action of orphenadrine in relieving muscular rigidity was on the thalamus. That orphenadrine may have some action on the diencephalon or the reticular formation has not been excluded but as already emphasised, its muscle relaxant property can

be /

be explained almost entirely by its action at the neuromuscular junction and probably also at the motor end plate region of the intrafusal fibres of the muscle spindles. The relief of chronic muscle spasm from various causes such as myositis, fibrositis, sciatica) by orphenadrine given orally (Finch, 1959) is almost certainly due to this peripheral muscle relaxant property. It seems unlikely that depression of spinal reflexes with consequent relief of skeletal muscular rigidity can be achieved by conventional oral dosage in man and in any case the action of orphenadrine on spinal reflexes is not constant.

Orphenadrine causes a mild to moderate degree of euphoria when given to patients. It is not clear how orphenadrine produces this action. It is possible that the euphoria is due to the effect of orphenadrine on the brain monoamine oxidases or on the metabolism of 5 hydroxytryptamine (5HT) in the brain. It may be of some significance that drugs which alter the levels of the free and bound 5HT in the brain, e.g. reserpine can produce both mental depression and Parkinsonism (Muller and his collaborators, 1955; Shuman, 1955; Munch-Peterson, 1956). Further study is required on the effects of orphenadrine and other anti-Parkinsonian drugs on brain 5HT and other amines.

The effect of orphenadrine on the fatigue induced by repeated indirect tetanisation of the hen's gastrocnemius muscle is of interest. /

interest. In an earlier section of this thesis attention has been drawn to the phenomenon of easy fatiguability of skeletal muscles in Parkinsonism. It has been shown that although hyoscine administered subcutaneously is probably the most effective drug for the relief of tremor and rigidity, the muscles tend to be more easily fatigued. This indicates that easy fatiguability is not altogether due to rigidity. Patients treated by the author with orphenadrine have often stated that they are less easily fatigued. This fact has recently been stressed by Dutch investigators (Bailly-Salin et al., 1961). One of their patients interpreted the meaning of Disipal (the trade name for orphenadrine) as "dissipation of fatigue". It is not known how orphenadrine produces this effect on fatigue either in human subjects or in experimental animals. Bijlsma et al (1956) showed that in frogs, orphenadrine caused vasodilatation. This would have offered an easy explanation but for the findings of the present writer that in the perfused rat's hindquarters, orphenadrine caused vasoconstriction. However, the action of orphenadrine on the blood vessels of skeletal muscles in intact animals has not been determined. Further studies are required to assess the role of increased muscle blood flow in the relief of fatigue.

It is possible that orphenadrine may have an effect on carbohydrate metabolism especially that of lactic acid metabolism. It is well known that its accumulation in the muscle leads to fatigue. It may be that orphenadrine relieves fatigue by enhancing the activity of /

of lactic acid dehydrogenases with the result that more lactic acid is oxidased and the fatigue relieved. It may however increase the synthesis of adinosine triphosphate (A.T.P.). Further studies on these aspects are indicated. The skeletal muscle relaxant property of orphenadrine may also play a part in the relief of fatigue. In the human subject there is little doubt that the euphoria produced by orphenadrine may favourably influence muscle fatigue. Under the influence of orphenadrine some Parkinsonian patients become less aware of their disabilities and may attempt physical effort of which they are quite incapable. Schwab and Prichard (1951), writing on the neurological aspects of fatigue, made the important point that fatigue does not necessarily mean that the muscle is incapable of further immediate response; more often it signifies an increasing conscious desire to stop the action. On the other hand a strong desire to complete the action will result in a prolongation of the period before voluntary fatigue sets in. Thus the euphoria produced by orphenadrine may increase the patient's "will power", and so delay the onset of fatigue. Perhaps the drowsy and dazed state produced by hyoscine decreases "will power" and thus tends to produce a state of easy fatiguability.

It has been shown that drugs which relieve Parkinsonian rigidity do not necessarily have the same mechanism of action. Orphenadrine has been shown to have neuromuscular blocking activity while benzhexol and "UK. 738" (in the limited number of experiments performed) have /

have little or no effect on the neuromuscular junction. Benzhexol probably produces its effects primarily by a central action. The recent case report by Singh (1961) is of interest. A 47 year old woman suffering from post-encephalitic Parkinsonism had had no relief from benzhexol hydrochloride (10 mg. daily) and in a fit of depression swallowed 75 mg. of the drug. On admission to hospital she was confused and agitated but the Parkinsonian rigidity and tremor had completely disappeared. She was found however to have signs of cerebellar dysfunction, namely slurred speech, coarse horizontal nystagmus, and intention tremor. About 24 hours later these signs had disappeared but the Parkinsonian rigidity and tremor had returned. In Chapter I (General Introduction) it was noted that the cerebellum was concerned with the maintenance of muscle tone probably by controlling the gamma effernet discharge to the skeletal muscles (Granit, Holmgren and Merton, 1955). Although Singh did not comment on the significance of the cerebellar dysfunction in his patient, these findings suggest that the relief of Parkinsonian rigidity by benzhexol may be due (at least in part) to a depressant action on the cerebellum thereby reducing the gamma efferent discharge. De Maar (quoted by Bijlsma, 1956) found that benzhexol depressed spinal reflexes in cats although in a few experiments using benzhexol (0.25 mg. to 1.0 mg. per kg.), an effect on spinal reflexes could not be demonstrated by the present writer. If benzhexol depressed spinal reflexes this could also account for its effect on muscular rigidity.

"UK. 738" probably produces its effect by a central depressant action /

action on the diencephalon and on the brain stem. It has little or no neuromuscular blocking activity. Thus 10 µg. per ml. of orphenadrine produced about 40 per cent block in a rat phrenic nerve diaphragm preparation while the same dose of "UK. 738" produced no neuromuscular blockade. The clinical dosage of orphenadrine and "UK. 738" are 100 mg. and 4 mg. respectively. Thus even in such relatively high concentration "UK. 738" showed no neuromuscular blocking activity.

SCREENING TESTS FOR DETECTING DRUGS WHICH MAY BE OF THERAPEUTIC VALUE IN PARKINSONISM.

(a) The use of inhibition of the flexor reflex in thalamic animals as a screening test.

Hyoscine has been shown to depress spinal polysynaptic reflexes in thalamic animals but not decerebrated or decapitated (spinal) animals (Teuchmann, 1949). This was rightly interpreted to mean that the site of action of hyoscine is at the level of the diencephalon. It was thought that all drugs used in the treatment of Parkinsonism owe their therapeutic efficacy to a hyoscine-like action on the diencephalon. De Maar (1956) and Bijlsma (1956) concluded that the depression of the flexor reflex in thalamic animals might be a useful screening test for anti-Parkinson drugs. When a drug has a significant depressant action on spinal reflexes in spinal animals or when it has a significant neuromuscular blocking action in the dose range that /

that blocks the spinal reflexes, this test, however, is of no value in deciding whether a drug has its action at the diencephalic level or lower down the cerebrospinal axis. Furthermore, as already stressed, the lack of a depressant effect on the diencephalon does not mean that the drug cannot be of use in the treatment of Parkinsonism as the rigidity can be relieved by other means.

(b) Depression of activation of the E.E.G. produced by stimulation of the brain stem reticular formation as a screening test.

Rinaldi and Himwich (1955) found that atropine prevented the appearance of E.E.G. activation (low voltage fast waves) when the brain stem was stimulated. They regarded atropine as the best anti-Parkinsonism drug and found that it had the maximal effect (4+) in preventing this E.E.G. activation, followed by diphenydramine, benzhexol and caramiphen (3+), then diethazine (2+) and mephenesin (1+), while reserpine and amphetamine did not cause any depression but rather increased the activating influence of brain stem stimulation. They suggested that the prevention of the alerting reaction in the E.E.G. may be used as a pharmacological screening test for drugs likely to be of use in Parkinsonism.

It is clear that while this may be a useful test, all drugs likely to be of use in the treatment of Parkinsonism cannot be selected by means of this test. Curare and Mephenesin do not cause any changes in the E.E.G. (Goodman and Gilman, 1958; Berger, 1949; Stephen and Chandy /

Chandy, 1947) and yet these drugs reduce Parkinsonian rigidity. Furthermore, it is now established that there may be a lack of correlation between the effects of a drug on electrical activity and on behaviour (Bradley and Elkes, 1957; Elkes, 1958). Thus atropine causes a high voltage slow activity which in general terms is not unlike that seen in sleep; the animals however, are alert and awake and may show signs of excitement and over-activity. Physostigmine causes the appearance of low voltage fast activity but the animals are quiet and may apparently be asleep. Amphetamine however gives rise to a low voltage fast activity and correspondingly the animals are alert, restless and excited. The influence of a drug on the cephalic and caudal effects of electrical stimulation of the brain stem are therefore not always identical. With regard to Parkinsonism the more important aspect of brain stem stimulation to study is the caudal effect, i.e., the effect on the spinal cord and the skeletal muscles especially with regard to muscle tone and tremor. Study of the cephalic effects of brain stem stimulation is less important and in any case does not yeild information upon the events taking place in the skeletal muscles. It can therefore be appreciated that the test proposed by Rinaldi and Himwich is not altogether satisfactory and cannot serve as a universal screening test. Depression of the effects of brain stem stimulation on skeletal muscle activity using an electromyogram will be of greater value as a screening test although it must be emphasised that some of the drugs showing a depressant /

depressant activity may prove to be of no clinical value. This test does not indicate where the precise site or sites of action of the drug are, as this may be anywhere between the reticular formation and the skeletal muscle.

(c) Inhibition of tremor induced by Tremorine (1, 4-dipyrolidino-2-butyne) (Everett, Blockus and Sheppard, 1956; Blockus and Everett, 1957) as a screening test.

There are various objections to the use of this test as a screening test. In the first place the mode of action of Tremorine is unknown although it has been shown by Ahmed and Taylor (1959) that the drug induces tremor which is very similar in its physical characteristics to that of Parkinsonism; both are of the sinusoidal type. Secondly, Desci, Vārszegi and Mēhes (1961) have shown that tolerance to Tremorine is virtually complete after 5 to 6 administrations of 6 to 18 mg. per kg. of the drug at two-day intervals! Sensitivity, however, returns on discontinuing its administration for two to three weeks. This development of tolerance is a serious obstacle as it may lead to wrong conclusions as to the potential usefulness of a drug in Parkinsonism.

(d) Inhibition of tremor induced by Nicotine (Bovet and Longo, 1951) as a screening test.

Here again we do not know how nicotine produces tremor in experimental animals. More important still, not all drugs which have been /

been found to be of therapeutic value in Parkinsonism inhibit nicotine-induced tremor. Thus atropine and even hyoscine which is probably the most effective drug for the relief of tremor and rigidity of Parkinsonism do not inhibit the tremor induced by nicotine.

CONCLUSION

From the above discussion, it is clear that none of the screening tests so far devised is universally applicable, since drugs giving negative results with one of the tests can still be effective in the treatment of Parkinsonism. The most rational way to investigate the mode of action of drugs of therapeutic value in Parkinsonism and of new chemical substances is to study their effects at the key points (indicated in Fig. 88) in the chain of events leading to the production of rigidity or increased tonus. A definite depressant action at any one of these points will indicate that the substance is of potential value in the treatment of Parkinsonism. There is no doubt that this method, using a physiological approach, is best and it is by this means that the mode of action of drugs of therapeutic value in Parkinsonism can be elucidated more precisely. The afferent spindle discharge is the final regulator of skeletal muscle tone and a plea is made that the effect of drugs on afferent spindle discharge should be studied. Substances which depress afferent spindle discharge either by preventing depolarisation at the end plate region of the intrafusal fibres or by a direct depressant action on afferent nerves /

nerves from muscle spindles are likely to be of potential value. Suxamethonium is a good research tool in this respect.

Because excessive salivation is frequently present in Parkinsonism it is desirable that anti-Parkinsonism drugs should possess atropine-like anti-muscarinic activity. This anti-muscarinic activity should, however, be much less than that of atropine otherwise patients will complain of excessive dryness of the mouth, blurred vision from mydriasis, and constipation. It is therefore essential to compare the anti-sialogogue activity, the spasmolytic activity on guinea pig ileum and the mydriatic action of the drug with those of atropine. It must however not be assumed (as appears often to be the case) that atropine-like activity on the guinea pig ileum (spasmolytic activity) means that the drug will have a skeletal muscle relaxant property.

It is now well recognised that two or more drugs sometimes produce a better therapeutic effect in Parkinsonism than a single remedy (Schwab and Tillman, 1949; Gillhespy, 1960). Controlled studies on this aspect have not been carried out but clinical experience in some of the patients investigated suggests that true synergism exists between orphenadrine and benzhexol. Although the anti-Parkinsonian drugs do not have a common chemical basis for their action and the pharmacological actions may differ from one another, the fact that there is a multiplicity of effective sites of action explains the synergism of effect between many drugs used in the treatment of Parkinsonism. It can readily be understood that

because of disturbing side-effects, or because of toxicity it is not often possible to exceed a particular dose level for any one drug. At this dose level the drug may only partially relieve the rigidity and tremor. In order to produce greater degree of relief, administration of another drug or drugs will be required. If the toxicity is due to excessive action at a particular site then clearly drugs having the same mode of action at this site should not be used while drugs relieving the rigidity by their action at a different site will be indicated. It is therefore possible to increase the relief given to the patient without increase in toxicity by giving two drugs such as orphenadrine and benzhexol or UK. 738.

Atropine, hyoscine and the galenical preparations belladonna and stramonium have a very much higher anti-muscarinic activity than the newer synthetic drugs used in the treatment of Parkinsonism. These synthetic drugs, benzhexol, orphenadrine, etc., while relieving rigidity and tremor, may not materially affect the hypersalivation if this is excessive. In such cases, instead of increasing the dose of these synthetic drugs, with the risk of producing disturbing side-effects, clinical experience has shown that administration of a small dose of atropine or a galenical preparation can relieve the hypersalivation without producing toxic effects. The only difficulty is the possibility of rather rapid emergence of tolerance with the result that larger and larger doses have to be administered. Synergism may exist between drugs which have primarily a thymoleptic action (even though /

though they have no skeletal muscle relaxant property) and the standard preparations of therapeutic value in the treatment of Parkinsonian tremor and rigidity. The feeling of well-being so produced is good for morale, especially in depressed patients and it tends to lessen fatigue which is a common complaint in Parkinsonism.

SUMMARY

Pharmacological studies with orphenadrine show that it has a definite neuromuscular blocking action in the frog and in the rat. In the cat, however, the neuromuscular blocking action is very much less. It is suggested that one of the ways by which orphenadrine reduces Parkinsonian rigidity is through its peripheral skeletal muscular relaxant property. The euphoric action noted in human subjects and the peripheral skeletal muscular relaxant property contribute to the favourable effect of this drug on the muscle weakness and easy fatiguability in patients suffering from Parkinsonism.

Benzhexol and "UK. 738" do not possess a neuromuscular blocking action. Ethopropazine, on the other hand, shows a neuromuscular blocking action in the rat. It is possible that one of the ways whereby ethopropazine relieves rigidity is through its peripheral skeletal muscular relaxant action.

It is the opinion of the writer that a depressant action on the cerebellum is probably one of the ways by which benzhexol relieves the rigidity of Parkinsonism.

In the cat, orphenadrine antagonises the neuromuscular block induced by suxamethonium. This suggests the possible use of orphenadrine as an antidote to suxamethonium when the latter has caused complete and prolonged neuromuscular block in human subjects. It is also suggested that orphenadrine may be of therapeutic value in the prevention of muscle pain after the administration of suxamethonium.

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SUMMARY

CLINICAL AND PHARMACOLOGICAL STUDIES IN POST ENCEPHALITIC PARKINSONISM

Chapter I. General Introduction

This chapter deals mainly with the control of skeletal muscle tone and the physiology of tremor. The clinical features and treatment of Parkinsonism are also discussed.

Chapter II. Crises in Post-Encephalitic Parkinsonism

A study of 67 patients with post-encephalitic Parkinsonism revealed three types of crises: they can be described as oculogyric, sweating and breath-holding.

The clinical accompaniments of oculogyric and sweating crises are described. Attention is drawn to the vasomotor changes which occur during severe oculogyric and sweating crises and to changes in mood during oculogyric crises.

The pathogenesis of the oculogyric crisis is discussed. It is suggested that ocular deviation is the consequence of a vestibulo-ocular reflex in patients with brain stem lesions involving the vestibular pathway. The emotional changes which accompany oculogyric crises are probably the result of stimulation of the diencephalon.

The role of emotion in precipitating oculogyric crises is confirmed. When emotion is known to play a part, it is suggested that the mechanism includes a conditioned reflex. Alternatively it may be that /

that the onset of emotional disturbance sometimes permits activity in the vestibulo-ocular reflex; activity which in the non-emotional state is materially inhibited.

Chapter III. Drug Therapy in the Crises of Post-Encephalitic Parkinsonism

The treatment of severe oculogyric and sweating crises in 11 patients with post-encephalitic Parkinsonism has been studied.

The value of 200 mg. sodium phenobarbitone given intramuscularly or sodium amylobarbitone 200 to 300 mg. given orally was assessed. Neither of theseforms of treatment affected the natural course of crises when these were in the category classified as "severe".

A therapeutic trial was carried out to evaluate sodium phenobarbitone 150 mg. given intravenously and 50 mg. given intramuscularly in severe crises, using injections of normal saline as the control. Relief was obtained in 20 to 40 minutes after these injections of the barbiturate. Injections of normal saline were ineffective. It is suggested that in severe crises sodium phenobarbitone injected intravenously is the treatment of choice. Although parenteral injections of hyoscine hydrobromide is effective in controlling severe oculogyric crises, the use of intravenous sodium phenobarbitone is to be preferred. The use of parenteral injections of atropine sulphate is not recommended.

The prophylactic value of sodium phenytoin was determined in 5 patients suffering from severe oculogyric crises. This drug altered the /

the character of the oculogyric crisis but did not reduce its frequency or severity.

The writer has no experience of oculogyric crises induced by drugs of the phenothiazine series such as Perphenazine, but there appears to be a prima facie case for the intravenous injection of sodium phenobarbitone in this type of medical emergency.

Chapter IV. The Electroencephalogram in Post-Encephalitic Parkinsonism

Electroencephalographic study of 30 patients suffering from post-encephalitic Parkinsonism showed that over half of them have low voltage alpha rhythm (below 40 μv.). It would appear that in post-encephalitic Parkinsonism the phenomenon of low voltage E.E.G.'s is most frequently seen in patients who are known to be liable to oculogyric crises and in those who suffer from severe rigidity and who are incidentally often bedfast.

There was a very high incidence of theta activity most prominent frontally. The records of 9 patients were regarded as definitely abnormal because of the presence of high voltage theta and delta activity. Abnormal records were more common in patients who suffer from severe rigidity.

The E.E.G. during an oculogyric crisis has the following characteristics: anteriorly there are high voltage spike potentials, in the other areas there is a general lowering of voltage, beta activity may become /

become more obvious.

Administration of 1.5 mg. of prostigmin intramuscularly had little or no effect on the E.E.G.

Chapter V. Deformities in Post-encephalitic Parkinsonism

The deformities of the hand in post-encephalitic Parkinsonism have been classified as Types I, II and III. Type I (main d'accouchûer deformity) is the most common form.

Talipes equino varus deformity is the common deformity of the foot in Parkinsonism.

Scoliotic deformity of the spine, especially of the cervical spine, is common. The scoliosis is usually concave to the less rigid side.

The factors of importance in the pathogenesis of deformities include: skeletal muscular weakness, rigidity and involuntary muscle spasms. Muscle weakness is the most important factor. It is emphasised that deformity is not due to the action of the rigid muscles (as is commonly thought), but results from an uncounterbalanced action of the stronger and less rigid muscles. The opposing weaker and more rigid muscles are lengthened as a result.

It is suggested that the effect of posture is probably the most important factor responsible for dribbling of saliva.

The use of splints and lamb's-wool in the management of some types of deformities is discussed.

Chapter VI /

Chapter VI. Assessment of Drug Therapy in Parkinsonism

The relative therapeutic value of orphenadrine and "UK. 738" (Sandoz) were studied by means of a double blind trial. Orphenadrine 100 mg. thrice daily was found to be about three times as effective as "UK. 738" 4 mg. t.d.s.

The methods of assessment of the efficacy of drug therapy in Parkinsonism are reviewed and the value of objective measurements is demonstrated. It can be said that the results of objective measurements usually run roughly in parallel with an assessment of the patient's condition as determined by the clinician - and especially when the initial degree of disability is moderate.

By means of "acute" experiments it was shown that after oral administration of orphenadrine, peak activity occurred in about two hours whereas peak activity due to benzhexol occurred in two to three hours. It was not possible to demonstrate clearly defined peak activity for the drug "UK. 738". Failure to carry out the objective tests at the time of maximal activity of drugs is an important source of fallacy in clinical trials designed to assess the relative merits of preparations used to combat the disabilities associated with Parkinsonism.

Chapter VII. The sites and mode of action of orphenadrine and other drugs used for the relief of rigidity and muscle weakness in Parkinsonism

Pharmacological /

Pharmacological studies with orphenadrine show that it has a definite neuromuscular blocking action in the frog and in the rat. In the cat, however, the neuromuscular blocking action is very much less. It is suggested that one of the ways by which orphenadrine reduces Parkinsonian rigidity is through its peripheral skeletal muscular relaxant property. The euphoric action noted in human subjects and the peripheral skeletal muscular relaxant property contribute to the favourable effect of this drug on the muscle weakness and easy fatigu-ability in patients suffering from Parkinsonism.

Benzhexol and UK. 738 do not possess a neuromuscular blocking action. Ethopropazine, on the other hand, shows a neuromuscular blocking action in the rat. It is possible that one of the ways whereby ethopropazine relieves rigidity is through its peripheral skeletal muscular relaxant action.

It is the opinion of the writer that a depressant action on the cerebellum is probably one of the ways by which benzhexol relieves the rigidity of Parkinsonism.

In the cat, orphenadrine antagonises the neuromuscular block induced by suxamethonium. This suggests the possible use of orphen-adrine as an antidote to suxamethonium when the latter has caused complete and prolonged neuromuscular block in human subjects. It is also suggested that orphenadrine may be of therapeutic value in the prevention of muscle pain after the administration of suxamethonium.