THESIS

on

OBSERVATIONS ON THE SERUM POTASSIUM WITH SPECIAL REFERENCE TO MYOTONIA.

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by

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CONTENTS.

"Without speculation there is no good or original observation" - Charles Darwin.

There is no doubt that during the present century the advances in biological knowledge have been more fundamental than at any previous stage in the history of biology. The study of form and movement has reached its zenith, and there has been an imperceptible change to the realisation that anatomy, morphology, histology are but the external manifestations of the chemical changes that form the basis of biological activity. In no branch of biology has this change been more pronounced than in neurology, and happily it has been equally productive of therapeutic advance, which is the ultimate aim of medicine. The gibe of the cynic that the study of neurology, however admirable and fascinating an academic pastime it may be, is of little use to the sufferer from disease of the nervous system, is even less true than it was. Progress in neuro-surgery has been spectacular, but by its very nature it must be approaching its limits. Great advances have been made in our knowledge of the important /

important relation of ultramicroscopic viruses to various diseases of the nervous system, but, so far, they have not led to any equivalent advance in treatment.

There are, however, two branches of neurology, of which in the last decade our understanding has increased enormously, which hold out the promise of even greater developments in treatment in the future. In the first group, the importance of the association of disorders of nutrition with certain lesions of the nervous system has been realised, and has not only led to many advances in treatment, but has opened up a vast new field for investigation. The second group, certain aspects of which form the main subject of this thesis, is composed of familial periodic paralysis, myasthenia gravis and the myotonias. Before considering this last group, however, I consider it worth while to give a brief summary of our present knowledge of the first group in order that we may view in its proper perspective the trend of neurological advance as exemplified by a consideration of the diseases of the neuro-muscular system which I have mentioned.

SUMMARY OF PRESENT KNOWLEDGE OF ASSOCIATION OF DISORDERS OF NUTRITION WITH DISEASES OF THE NERVOUS SYSTEM.

Lettsom (1786), the first to describe alcoholic polyneuritis, drew attention to the frequent association of gastro-intestinal disturbances and distaste for food, but regarded the polyneuritis as a direct neurotoxic effect of alcohol. Following researches carried out from 1890 onwards in Java, Christian Eijkman (1897) reported classical experiments, which showed that deficient nutrition could give rise to degenerative lesions in the peripheral nerves. He came to the conclusion that the disease beri-beri resulted from the continuous consumption of decorticated (polished) rice. Gastric achlorhydria is thought to favour the development of beri-beri, particularly when the diet is restricted (Cowgill, 1934). It now seems definitely established that beri-beri in man and experimental beri-beri in animals can be adequately explained on the basis of a lack of vitamin B_1.

Shattock (1928) was probably the first to suggest that alcoholic polyneuritis was caused by a failure to /

to take or to assimilate food containing sufficient vitamin B. Deficient intake of vitamin B_1 results from neglect, anorexia, nausea and vomiting. Requirements are increased by the high caloric value of the alcohol, which acts as a pure carbohydrate. At the same time absorption is impaired by the direct action of alcohol on mucous membranes and the destructive effect on alimentary enzymes (Blotner, 1936).

In a similar manner the polyneuritis of pregnancy is due to deficient absorption of vitamin B_1 owing to poor assimilation due to low gastric acidity, nausea and vomiting: the demands are probably increased owing to a raised metabolism, foetal demands, and the use of a diet rich in carbohydrates but poor in vitamin B_1 content. In coeliac disease, ulcerative colitis, pyloric stenosis, and faulty gastroenterostomy, absorption of vitamin B_1 may be so reduced as to produce polyneuritis. Polyneuritis may occur as a result of wrong dietetic treatment of peptic ulcer, and from deficient intake in gastric carcinoma. Complete achlorhydria is present in many cases of obscure polyneuritis (Russell, 1936).

It /

It is probable that subacute combined degeneration of the cord, like pernicious anaemia, is the result of a nutritional deficiency based on a gastric defect. Hurst (1934) suggested the name "neuropoietin" for a substance in liver extract differing from the haemopoietic principle. Anahaemin, the most highly concentrated liver extract, does not contain any vitamin A or B_1. But in some cases of pernicious anaemia there is no doubt that a vitamin B_1 deficiency is responsible for some of the peripheral nervous signs (Russell, 1936a). Vitamin B_1 has no effect on the lesions in the spinal cord, but therapeutic control of subacute combined degeneration of the cord can be established by the use of a water-soluble fraction of liver and vitamin B_1.

Mellanby (1934) called attention to the repeated statements of Buzzard and Greenfield concerning the similarity of the nerve lesions of the spinal cord in subacute combined degeneration of the cord to those of the spinal cord in nervous ergotism, pellagra and lathyrism. Mellanby had produced experimentally, in puppies on a vitamin A deficient diet containing an excess of cereals, a degenerative condition in the spinal /

spinal cord taking the form of a demyelination, which is intensified by the addition of ergot (Mellanby, 1931). He also pointed out that the occurrence of pellagra, convulsive ergotism and lathryism during periods of extreme poverty, famine and drought, together with the experimental evidence, supports the view that they are all due to certain common factors: large quantities of food containing neurotoxic elements, in the absence of vitamin A or carotene, exert their influence on the nervous system. Mellanby (1934) further stated: "Differences in the type of neurotoxin may well explain the difference in the symptoms and the nervous lesions which form their basis. That, however, their aetiology is of a similar nature, with some factors in common, is almost certain from the close resemblance of the nervous lesions as described by neurological experts like Buzzard and Greenfield who, prior to the present work, constantly remarked on the close identity of the degenerative changes in the nervous system associated with these diseases." That is a wide conception, but advances come from such broad and imaginative views, and recent work on pellagra is of interest /

interest in this connection.

Although nicotinic acid appears to be a specific therapeutic agent for the mucous membrane lesions of pellagra (Spies, Cooper and Blankenhorn, 1938), there is as yet no evidence that it has any effect on the nervous lesions. In the case of pellagra described by Yudkin, Hawksley and Drummond (1938), which yielded rapidly to treatment with a filtrate factor obtained by repeated adsorption of liver extracts with fuller's earth, there were no physical signs of derangement of the nervous system, although the patient had mild mental symptoms described as a neurosis: this patient gave normal responses to the dark-adaptation test, which, therefore, excluded any possibility of vitamin A deficiency. It may well be, then, that the spinal cord changes in pellagra result from deficient absorption of vitamin A consequent on the mucous membrane lesions due to lack of the pellagra-preventing factor.

Degenerated fibres in the spinal cord cannot be regenerated under any known condition, but there is much evidence to indicate that vitamin A lack is a factor in the production of the cord changes in pellagra, convulsive ergotism, lathyrism and subacute combined /

combined degeneration of the cord.

Demyelination of nerve fibres is also found in disseminated sclerosis, but the form and distribution differs widely from that found in subacute combined degeneration of the cord, pellagra, convulsive ergotism and lathyrism. Nevertheless, the frequent occurrence of retrobulbar neuritis as an early symptom of disseminated sclerosis is well known and suggests the possibility of some form of dietary deficiency. The eyes are specially susceptible to vitamin A deficiency, the manifestations being variable and including xerophthalmia and night blindness. It is also possible that some forms of retrobulbar neuritis are due to lack of vitamin A. Moore (1930, 1932) described outbreaks of partial loss of central visual acuity in children attending certain mission schools in West Africa. The children recovered on a diet containing marmite, cod liver oil, malt and iron tonic. Moore thought the trouble was due to vitamin B deficiency, but Mellanby attributed the cure to the Vitamin A in the diet. The association of retrobulbar neuritis, certain forms of which can be cured by dietary agents, with disseminated sclerosis, has led to the suggestion that the latter may be helped in a similar /

similar way. Sir Edward Mellanby, using a high vitamin A diet claimed great improvement in early cases and a stationary condition in more chronic cases; and curative effects from the administration of whole liver in disseminated sclerosis have also been described (Goodall and Slater, 1931). Though the problem is far from clear at present, it may well be that disseminated sclerosis is a deficiency disease of some kind.

In this brief survey enough has been written to demonstrate the enormous importance of adequate nutrition in the prevention of certain diseases of the nervous system. And it is well to remember that in temperate climates diseases of deficient nutrition are more frequently caused by gastro-intestinal disturbances affecting the assimilation of food than by inadequate diets (Straus, 1934). The position of vitamin A is still sub judice, but the therapeutic value of "neuropoietin" and vitamin B_1, both best given parenterally, is now undisputed. The way is open to a vast field of investigation, and many neurological problems will, no doubt, be solved on the lines I have just indicated.

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FAMILIAL PERIODIC PARALYSIS, MYASTHENIA GRAVIS AND THE MYOTONIAS.

Familial periodic paralysis, myasthenia gravis and the myotonias appear at first sight to form a small group of rare and unrelated diseases of the nervous system, and it would seem that any advances in their treatment cannot be of the same importance as the recent developments in neuro-surgery and in our knowledge of the relation of disorders of the alimentary system to diseases of the nervous system. But the therapeutic advances in these diseases are very important, because they emphasise a change in the line of attack in neurology, from morphology to biochemistry: and they hold out the hope that investigation of the mode of action of these new agents of treatment may throw some light on the many obscure problems of neurology.

Furthermore, there is some justification for considering them as a group. They all express themselves clinically as disorders of the neuro-muscular system; yet, with the possible exception of myasthenia gravis, no structural changes have been found in the central or peripheral nervous system. In myasthenia gravis the only changes found within the nervous system are slight atrophy of the nerve cells /

cells which supply long paralysed muscles, and these changes are certainly not primary (Collier, Adie and Walshe, 1937). Secondly, histological changes in the muscles appear in all of them.

Again, there is the possibility that some disturbance of endocrine metabolism is the basic trouble in all of them. In myasthenia gravis "the one clinical association which cannot be ignored is with exophthalmic goitre, for not only may myasthenia follow that malady, but the ophthalmoplegias which occur in Graves's disease bear no small resemblance to those of myasthenia" (Collier, Adie and Walshe, 1937). And in some cases of myasthenia gravis "a large persistent thymus gland, showing proliferative and degenerative changes, or thymic rests showing similar changes, has been found." Shinosaki in a review of twenty-four cases of familial periodic paralysis found that fifteen were associated with goitre, and also found in several patients a disturbance of the parathyroid gland. He advanced the theory that the disturbance in familial periodic paralysis is due to an underlying endocrine disorder. Dunlap and Kepler (1931) reported four cases of periodic paralysis in which there was hyperthyroidism, and relief of the hyperthyroid condition was followed by /

by disappearance of the attacks of paralysis. Morrison and Levy (1932) reported one case of familial periodic paralysis in which thryoidectomy led to diminution in the frequency and severity of the paralytic attacks.

In one form of myotonia, dystrophia myotonica, it is, of course, well recognised that among other signs of bodily dyscrasia, atrophy of the testicles is almost constant.

Again, permanent muscular atrophy or paralysis may appear in all these diseases. In myasthenia gravis a permanent paralysis, sometimes associated with atrophy of the muscles, may locally succeed the variable paralysis. Permanent muscular weakness with atrophy developed in two of Holtzapple's cases of familial periodic paralysis. Oppenheim (1901) described the slow development of muscular atrophy, especially localised in the thigh and buttocks in a case of periodic paralysis, and muscular atrophy developed in four of the family with periodic paralysis described by Biemond and Daniels (1934). Atrophy of muscles is, of course, a clinical feature of dystrophia myotonica and is recognised in its alternative name, myotonia atrophica. The extent and /

and intensity of the muscular atrophy, as of the myotonia, varies greatly.

Familial periodic paralysis and the myotonias are familial and hereditary diseases, and the age of onset is in early life often before puberty. Myasthenia gravis is not hereditary and the onset is usually later in life, in the third decade.

There is further evidence for a possible relationship between familial periodic paralysis, myasthenia gravis and the myotonias in the observations of several writers. MacLachlan (1932) described the occurrence of muscular dystrophy (dystrophia myotonica) in members of a family who suffered from familial periodic paralysis. There were six patients with periodic paralysis in three generations of this family, and the dystrophia myotonia occurred in certain members of the family not suffering from the periodic paralysis. Again, MacLachlan, in discussing the aetiology of familial periodic paralysis, said "some writers have stressed an analogy with myasthenia gravis, as in some cases of that disease attacks of paralysis lasting a few days and resembling those of family periodic paralysis have been described by Collins and others." Schoenthal (1934) has also made some pertinent observations. He wrote: "Two groups /

groups of diseases seem to show a relation to family periodic paralysis. The first is that of hereditary myopathies, such as progressive muscular dystrophy, myotonia congenita (Thomsen's disease) and myasthenia gravis. A few cases have been described in which symptoms of one of these diseases appeared in patients with periodic paralysis (Bernhardt, 1896). The other group which is characterised by its paroxysmal character, is the migraine-epilepsy group." I shall have more to say later concerning the relation of familial periodic paralysis to migraine.

There is, then, considerable evidence supporting my view that familial periodic paralysis, myasthenia gravis and the myotonias may justifiably be considered as a group. Furthermore, although these diseases have been recognised for about sixty years, little was known about the treatment of any of them until quite recently when, within the short space of three years, by the discovery of the use of prostigmin in myasthenia, potassium in familial periodic paralysis and quinine in myotonias, the most remarkable advance yet known in the treatment of each of them was made. The mode of action of quinine in myotonia, prostigmin /

prostigmin in myasthenia gravis and potassium in familial periodic paralysis is discussed in this thesis.

It is also part of my thesis to discuss these diseases in relation to the potassium ion which has a definite clinical effect on each of them.

I also intend to describe and discuss certain experiments and observations on the serum potassium, particularly with reference to three patients with myotonia. Some clinical observations are also made concerning these three myotonic individuals. And, lastly, some personal speculations in connection with diabetes and migraine are presented and discussed in relation to the serum potassium.

HISTORICAL SUMMARY.

The earliest cases of myasthenia gravis were described as "bulbar paralysis without discoverable anatomic change." Wilks (1877) in a paper published in Guy's Hospital Reports, described a case of bulbar paralysis in which no anatomical changes were found after death. This is the first reference to myasthenia gravis to be found in the literature, but the term was not then in use. Strumpel used the term "asthenic bulbar palsy," but the myasthenia is not confined to the bulbar muscles. Erb (1879) described a peculiar form of bulbar disease which was evidently myasthenia gravis. Two further cases were described in 1887 (Oppenheim, Eisenlohr). During the following years further cases were described and the disease was variously known as Erb's disease, Erb-Goldflam disease and the Hoppe-Goldflam symptom complex. Tolly then proposed the term "myasthenia gravis pseudo-paralytica," and in 1900 Dr. Harry Campbell and Professor Edwin Bramwell suggested "myasthenia gravis" for short and this term has remained. The name was, therefore, not finally established until over twenty years after the disease had been recognised as a clinical entity.

It /

It is a little difficult to decide which was the first authentic case of familial periodic paralysis. The honour is accorded by some to Cavaré who, in 1853, described paralytic attacks in a woman of twenty-four under the title "Observation d'une paralysie generale du sentiment et du mouvement affectant le type intermittent." Somewhat similar cases were described by Romberg (1857), and by Hartwig (1874) in his inaugural address at Halle under the title of "Intermittent spinal Paralysis." Cases resembling these were described by Samuelsohn (1876), Gibney (1882) and Schachnowitsch (1882). The cases described by Cavaré, Romberg, Hartwig and Gibney appear to have been relieved by quinine, and there is some doubt as to whether they were not really suffering from malaria. The question of hysteria has been raised in connection with Samuelsohn's patient. To Westphal (1885), therefore, who described an undoubted case and who gave the first detailed descriptions, is generally accorded the honour of establishing the disease variously known as family periodic paralysis, paroxysmal paralysis and myoplegia periodica.

By /

By the single word myotonia I include mytonia congenita and myotonia atrophica: I am not including myotonia acquisita which appears to be related to post-neuritic muscular hypertrophy (Krabbe, 1934).

The first case of myotonia congenita is, of course, definitely fixed by Thomsen's original description in 1876 of the disease named after him (Thomsen, 1876). In the following years further cases were described and in 1886 the publication of Erb's monograph on Thomsen's disease aroused great interest in myotonia in general. This led to the publication of a number of cases differing from the classical description of Thomsen, in that the myotonia was associated with some degree of muscular atrophy. This curious combination of myotonia and atrophy was fully described for the first time by Delage in 1890, and thereafter isolated examples of this variation of myotonia congenita were described by various workers, among others by Palizaeus in 1897, and by Nogues and Sirol in 1899, in whose patient the symptoms of Thomsen's disease had been present since he was seventeen years old, the muscular atrophy not developing until he was twenty-eight. In 1900 Hoffmann wrote a paper in which he showed /

showed that muscular atrophy occurred in about nine per cent of cases of Thomsen's disease.

Many more cases in which muscular atrophy was associated with myotonia were published in the following years, and ,in 1909, Batten and Gibb, and Steinert independently, established the condition "myotonia atrophica" as an entity distinctly differentiated from myotonia congenita as described by Thomsen. Unlike earlier writers, who detected no uniformity in the atrophy, these observers found that the atrophy was constant in certain parts such as the face, the muscles of mastication, the sterno-mastoids, the muscles of the forearm and the peroneal muscles. In 1911 Greenfield described a family of thirteen brothers and sisters, of whom five suffered from myotonia atrophica, two with, and three without cataract, and two from cataract alone. In the same year further observations were published demonstrating the association of myotonia atrophica and cataract. Very soon other extra-muscular symptoms became apparent and Curschmann in 1912 stressed the significance of the associated atrophy of the testes, baldness and loss of body weight which were described. In 1902 Rossolimo had proposed the term /

term "myotonia atrophica" for those cases of Thomsen's disease in which atrophy was supposed to have supervened, but Curschmann in 1912 proposed the name, dystrophia myotonica, which has since been adopted in preference, as it imphasises the associated dystrophic phenomena. Dystrophia myotonica was recognised as a distinct disease apart from myotonia congenita, and it was not thought that certain patients with myotonia congenita might later develop dystrophia myotonica. Recent observations, however, such as those of Maas (1937) would seem to indicate that the demarcation between these two forms of myotonia is not so clear as it was formerly thought to be. A point of distinction was the later age onset of dystrophia myotonica, but, as Maas has pointed out, it often begins in childhood. These points will later be more fully discussed in connection with one of the patients with myotonia whom I have myself examined.

From these brief historical summaries it will be realised that myasthenia gravis, familial periodic paralysis and the myotonias have been known and recognised as clinical entities for about sixty years. /

years. During this time much has been added to our knowledge of the clinical signs and symptoms, course and prognosis of each of them; but we have remained completely ignorant as to their true causation, and were equally helpless in their specific treatment until five years ago, when the discovery of the use of prostigmin in myasthenia was quickly followed by that of quinine in myotonia, and potassium in familial periodic paralysis.

Attempts to establish the true pathology of these conditions were largely devoted to careful and painstaking studies of the morbid histology of the muscles in particular. Many descriptions of the changes found were published, some of them based on specimens obtained by biopsy; but the discovery of the use of prostigmin, potassium and quinine in these conditions has concentrated attention upon the neuro-muscular function, because primary pathological changes have not been found in the nervous system. It will be useful in the case of each of these diseases to give a short outline of the progress of knowledge concerning their aetiology and treatment.

Myasthenia gravis.

As long ago as 1900 Dr. Harry Campbell and Professor /

Professor Bramwell in a critical digest of myasthenia gravis considered the possibility of the disturbance being at the nervous end-plate, but this idea was discarded and they put forward the view that a toxin, probably of microbic origin, circulating in the blood acted selectively on the lower motor neurone at the axon, although no structural changes had been found in the axon.

By a process of exclusion, in that no structural changes had been found in the nerves, nerve-endings or muscles, that could be related to the symptoms, attention was directed to the myo-neural junction as the site of the lesion.

S. Nevin (1934) in a study of muscle chemistry in the normal and in muscular dystrophy, myasthenia gravis and myotonia, by chemical examination of excised muscle obtained by biopsy, failed to reveal any changes characteristic of myasthenia gravis. He suggested that future studies of the causation of myasthenia gravis should be directed to the excitatory transmission at the neuro-muscular junction rather than along metabolic lines. The treatment of myasthenia gravis had been on an entirely unsatisfactory empirical basis until 1930 when Dr. Harriet Edgeworth, herself a sufferer from this disease, /

disease, published her own personal observations on the beneficial effect of ephedrine which she had been taking for reasons unconnected with myasthenia. The known pharmacological actions of ephedrine are almost without exception the same as those of adrenalin, and, therefore, as Nevin pointed out, ephedrine is most likely to act at the neuro-muscular junction. Meanwhile following the introduction of glycine for the treatment of the muscular dystrophies, this remedy was applied to myasthenia gravis by Boothby (1934) and by Gros (1934) with some favourable results. Gros used glycine only, but Boothby used glycine and ephedrine together, and concluded that with this treatment most patients improved sufficiently to enable them to return to work. Natural remissions and ignorance of the true nature of the pathological upset, whether neural, muscular or humoral, made appraisement of remedies somewhat difficult, but there is little doubt that the use of glycine and ephedrine constituted a distinct advance in treatment. Furthermore, as mentioned earlier, attention was being directed to the neuro-muscular junction.

About this time, in June 1934, Dr. Mary B. Walker in a short letter to the Lancet described the definite /

definite improvement she had obtained in a case of myasthenia gravis by the use of physostigmine. She thought that the paralysis of myasthenia gravis bore some resemblance to that of poisoning by curare, and used physostigmine because it is an antagonist to curare. On February 8th, 1935, she demonstrated before the clinical section of the Royal Society of medicine a patient with myasthenia gravis in whom complete relief was obtained by the injection of Prostigmin, (an analogue of physostigmine manufactured by the La Roche Chemical Works, Ltd., and of which the formula is "dimethyl-carbamic ester of m-hydroxy phenyl-trimethyl ammonium-methyl sulphate). The patient was being given as much as 4 mgm. prostigmin without ill effect, although in other cases the same dose had caused severe diarrhoea and cardiac and respiratory distress. Dr. Walker found that, in comparison with physostigmine salicylate which she had previously used, the prostigmin had a less depressing effect on the heart, caused less nausea and vomiting and was probably safer in larger doses: it also caused less nausea hypodermically than orally. The coincident hypodermic injection of atropine lessened the unpleasant side effects of prostigmin.

Dr. /

Dr. Walker's results were quickly confirmed by E.A. Blake Pritchard (1935) on seven patients, and by L.P.E. Laurent (1935). As an example of the effect of prostigmin, one of Dr. Walker's patients was given 2.5 mgm. prostigmin and 0.66 mgm. atropine daily at 10 a.m. In five minutes this patient, formerly unable to do so, could sit up in bed, and in ten to fifteen minutes could walk two to three hundred yards. The effect of the drug was at its height in one hour, and began to wear off in six hours leaving behind some stiffness of the muscles. Laurent in addition tested another drug of the prostigmin group (methyl-phenyl carbamic ester of 3-oxyphenyl-trimethyl-ammonium-methyl sulphate) and found that, although Aeschlimann and Reinert (1931) had shown that it had no anti-curare action, the anti-myasthenic action was little short of prostigmin, the difference being a slower onset and shorter action.

Further confirmation of the beneficial effects of prostigmin was afforded by the observations of Cooke and Passmore (1936) on another patient with myasthenia gravis, and by many other observers (Lindsley 1935, Minski and Stokes 1936, Wade 1936, Marinesco, Sager and Kreindler, 1936, Winkelman and Moore, /

Moore, 1937). It is now definitely established that the use of prostigmin is the most marked improvement that has yet been made in the treatment of myasthenia gravis.

There are, however, certain disadvantages. Cooke and Passmore (1936), Foster Kennedy and Wolf (1938) and Minski and Stokes (1936) have all found a refractory period after several days treatment with prostigmin. Hyland (1936) warned against repeated administration lest it be followed by alarmingly increased weakness. Boothby (1935) pointed out the mental depression and greater weakness which followed its use and C.K. Russell (1937) warned against the dangers of the "let down" after five to six hours from the injection.

Meanwhile efforts were being made to establish the actual site of the neuro-muscular disturbance. Blake Pritchard (1933) using condenser discharges of high frequency (over eighty per second) had electrically stimulated the ulnar nerve of a patient suffering from myasthenia gravis. The myographic record he obtained from the tension developed in the flexor muscles of the fifth finger differed strikingly from that of the normal person, and from that of any other form /

form of muscular weakness except myasthenia gravis:-

Normal person. Myasthenia gravis.

He considered that the form of this curve provided direct evidence that the weakness in myasthenia gravis is due to a disturbance at the neuro-muscular junction.

Further, the work of Cowan (1936) indicated that neither nerve trunk nor muscle fibre is affected by prostigmin, so that by exclusion the site of its action must be the neuro-muscular junction. This has long been recognised in the case of curare.

Dale and Feldberg (1934) had shown that the normal transmission of nervous impulses from the motor nerve endings to the voluntary muscles is effected by the liberation of acetylcholine at the neuro-muscular junction. Using prostigmin Blake Pritchard (1935) restored the myasthenic curve to the normal form, while at the same time the patient's strength returned. This was confirmed by Lindsley (1935). Because of Dale and Feldberg's work these results suggested that an abnormality in the metabolism of acetylcholine is responsible for the muscular weakness of myasthenia gravis, /

gravis, and it seems probable that prostigmin acts either by aiding the liberation of acetylcholine or by preventing its too rapid destruction by the choline esterase normally present in the blood.

Further support for the view that the defect in myasthenia gravis is one of chemical transmission at the neuro-muscular junction is afforded by the observation that curare and prostigmin are mutually antagonistic. Normal muscular action can be preserved when poisonous doses of these drugs are exhibited together. According to Briscoe (1936) this can only be explained on the theory of chemical transmission of excitation.

In 1935 Drs. E. Stedman and W.R. Russell estimated the choline esterase content of the defibrinated blood of a number of patients with myasthenia gravis and also of some normal persons. They found a tendency to a low content of choline esterase in the blood of the myasthenic as compared with the normal controls. The content of the red blood corpuscles appeared to be normal, the low value being due to the lower serum content. If one assumes that the serum content of choline esterase is a measure of its concentration in the tissues it seems clear /

clear that myasthenia gravis is not due to an excessive destruction of acetylcholine by choline esterase. Work by Fraser, McGeorge and Murphy (1937) supports the view that the defect is in acetylcholine production.

Feldberg and Vartiaienen (1934), using the superior cervical ganglion of the cat, found that eserine (physostigmine) strongly sensitises the ganglion cells to injection of acetylcholine. They also found that the addition of potassium chloride to the perfusing fluid stimulated the ganglion cells, and that a dose of potassium chloride, not large enough to do so directly, "raised the excitability of the ganglion cells to preganglionic stimuli, to acetylcholine and to other chemical stimulants." The enhancement of the stimulating effect of acetylcholine by potassium ions was found to be "of the order of fifty per cent." Eserine was about sixteen to forty times more powerful than potassium. These considerations indicated the probable mode of action of physostigmin and prostigmin in myasthenia gravis, and also led Laurent and Walther (1935) to investigate the effect of potassium chloride by mouth in myasthenia gravis.

They /

They examined the blood of ten normal persons and of six myasthenics, and did not find any significant alteration in the level of serum potassium in either group. But they found that potassium chloride given in large doses (10 to 12 grammes) by mouth gives a demonstrable improvement in myasthenia gravis, and that in small repeated doses it is a useful adjuvant to prostigmin. Mary B. Walker (1935) confirmed Laurent and Walther's findings. On the other hand, Minski and Stokes (1936) found that with their cases potassium chloride had little adjuvant effect and increased the toxicity: and Wade (1936) used potassium chloride in doses up to twelve grammes a day without any result.

Familial Periodic Paralysis.

The earliest opinion expressed as to the nature of familial periodic paralysis was by Hartwig (1874) who suggested that the paralysis was due to an intermittent hyperaemia of the spinal cord. Samuelsohn (1876) suggested the condition was hysterical, but his patient is thought to have been suffering from true hysteria. Westphal (1885) suggested some form of toxaemia, and this view was supported by Goldflam (1891), who added that it was probably an auto-intoxication /

intoxication and placed the lesion in the muscle fibres and motor nerve endings. Singer and Goodbody (1901) found microscopical changes in the muscle in samples obtained by biopsy, but after studies of the blood, urine and faeces, failed to find any abnormality.

MacLachlan (1932), from a study of six cases without post mortem examination, thought that two factors are concerned in causing the attacks of paralysis: "(1) An abnormal constitution or diathesis in which there exists, in patients with a neuropathic inheritance, a condition of disequilibrium of the vegetative nervous system with evidence of periodic intoxication associated with abeyance of the digestive function and abnormal metabolism at the time of the attacks. (2) Some abnormality in the muscles themselves." This hypothesis was really a vague generalisation.

Biemond and Daniels (1934) came to the conclusion that there was no definite knowledge of the cause of the disease. They believed, from studies of the blood and urine during attacks, that the essential basis for an attack is to be found in an alteration /

alteration of the chemistry of the muscles. At the same time they remarked on the variation of the quotient of calcium to potassium in the blood, from 1:2 during an attack to 1:7 in the interval. The figures they found were:-

	Calc.	Potass.	Magnes.	Phosph.	Lactic acid.	
During attack	11.15	13.38	4.45	4.44	26.33	mgms. per cent.
During interval	10.69	17.87	3.49	5.88	47.7	mgms. per cent.

They stated: According to Kraus and Zondek this shifting should be related to an imbalance of the autonomic nervous system in the sympatheticotonic direction." They advanced their conclusion with the greatest caution as the attack during which blood was taken was a very mild one and the analysis was made only once. Although I cannot quite understand their mathematics of ratios, it is evident that they failed to realise the great significance of the drop in the level of the serum potassium to 13.38 mgms. per cent during the attack.

According to Biemond and Daniels only Goldflam found definite alterations in the muscles in the few cases which have been examined post mortem. /

mortem. Biemond and Daniels themselves examined two small pieces of the rectus femoris muscle obtained by biopsy from one of their patients. No definite pathological changes were found in either of the two specimens, one of which was obtained during a mild attack and the other during an interval. These authors concluded by saying that anatomical examination threw no light on the essential nature of the disease.

It may be said of familial periodic paralysis, therefore, that, although something was known about the circumstances under which attacks arose, nothing was known about their essential causation and no drug was known which would shorten an established attack, until Aitken, Allott, Castleden and Walker (1937) published their observations on their patient. They showed beyond any possibility of doubt that each attack was associated with a pronounced fall in the level of the serum potassium, and that attacks could be shortened by giving potassium salts. They had chemically examined the blood during attacks and in the intervals. The blood urea and sugar, the serum sodium, potassium, calcium, chloride, inorganic phosphorus, bicarbonate, non-protein nitrogen, albumen, globulin and total protein were all examined, and /

and the only change found was a significant fall in the level of the serum potassium during an attack.

These authors in discussing their findings said that they found in the literature only two previous references to potassium in connection with familial periodic paralysis. They referred to the reports by Biemond and Daniels (1934) and Herrington (1937). From a perusal of the literature, however, I have found several reports of cases in which potassium is mentioned, and in some of which the salt may have had a beneficial effect. I think these instances are worth mentioning as they indicate how the correct drug may be used for years empirically without realising the significance.

As long ago as 1901 Singer and Goodbody, in publishing their description of the first case of familial periodic paralysis published in Britain, stated: "Diuresis should be promoted by the exhibition of large quantities of water, or as a pleasant and efficient substitute, Imperial drink, while the bowels should not be allowed to become constipated. Drugs probably are not of much value, but if the attacks are frequent some digitalis or potassium acetate or citrate may be found useful." Any benefit derived from the above measures was probably due to the potassium /

potassium in the mixtures and in the Imperial drink.

Also in 1901, Sir Farquhar Buzzard described three patients of his, a mother and her two sons, whom he treated according to Dr. Singer's recommendations. The younger boy had fifteen attacks in nine days, during which his average daily output of urine was 25-30 ozs. He was then given for seven days three pints daily of the following mixture:-

R	Ac. tartrate of potash	℥ss
	Syrup	℥ij
	Lemon juice	℥ss
	Aq. distillata	℥xx

During this time he had twelve attacks and about 80 oz. of urine a day were excreted. In the next eight days there were eleven attacks, the output of urine being the same. Digitalis was then ordered, and the attacks became, if anything, more frequent. Again, any improvement there may have been, was probably due to the potassium in the drink and not to the diuresis which was claimed as the cause of the improvement. It is unlikely that diuresis increased the level of the serum potassium by making the blood serum more concentrated.

In 1902 Mitchell, Simon Flexner and Edsall described three patients with familial periodic paralysis. /

paralysis. Patient No. 1 had observed that citrate of potash had a favourable effect on attacks. As a prophylactic citrate of potash seemed to have some small but uncertain effect in patients Nos. 1 and 2 in doses of 45-60 grains a day. In patient No. 3 it did not reduce the frequency of the attacks. "Administered at the beginning of a seizure in repeated large doses, it certainly shortened and mitigated the paralytic period in all three patients." In patient No 3 attacks were very regular every seventh or eighth day lasting forty-eight hours. These were reduced to twenty-four hours by the continuous administration of potassium citrate. Potassium bromide shortened attacks in Nos. 1 and 2 but was no use in No. 3. Attacks were much less affected by potassium carbonate than by potassium citrate. Owing to a druggist's error No. 1 once had potassium chlorate: the result was not quite so favourable as with potassium citrate. Bicarbonate of soda was tried often, but had no apparent effect. It seems certain that potassium had a pronounced good effect in all these three patients.

Holtzapple (1905) who described the largest series (nineteen) of cases of familial periodic paralysis yet reported, found potassium bromide of use. /

use. "The dose of bromide, preferably of potassium, usually consisted of ʒss, with caffein cit. gr. i or ii." He said that the potassium bromide had an abortive influence, and hastened improvement when taken in paroxysm, and attributed the good effect to the bromide element of the salt. It is almost certain, however, that the potassium ion was the effective one.

Gardner (1912) reported on a patient of his, a young collier, whom he had observed for five years. This young man had frequent attacks of paralysis, generally at the weekend after hard exercise at football followed by beer and a good supper. Gardner put him on the following regime:-

1. No beer or rich food. Drink as much water as possible.
2. Mag. sulph. ʒ i in half a pint of hot water on rising in the morning.
3. Pil hydrarg gr. ii nocte, once a fortnight.
4. Tr. digit. ℥ iv, pot. acetate gr. xx, syrup ʒss, aq. menth. pip. ʒi
5. Caff. cit. gr. vii, pot.brom. gr. x, ac. hydrobrom. dil ℥ xx, syrup ʒss, aq. chlor. ʒss. (This last mixture with the bromides was given in deference to Holtzapple, whenever there was any warning of an attack).

He was told that after a football match he should eat a light supper and drink no beer but much water.

Following these instructions the patient had no attacks /

attacks for two years. Gardner attributed the success of these prescriptions to their diuretic action, and said that the bromides were probably useful because of their action in preventing sleeplessness. It will be noticed, however, that the prescriptions contained potassium.

As mentioned before, Biemond and Daniels (1934) in discussing the possibility of a disturbance of the autonomic system as the cause of attacks, noted that attacks occur at night when the Vagus is active and mention that "the shifting in the blood of the potassium, calcium and magnesium, and the change in the blood sugar and sweating suggest an autonomic imbalance." They also found a blood serum potassium level of 13.38 mgm. per cent during an attack and 17.87 mgm. per cent during an interval, but they failed to appreciate the significance.

Herrington (1937) reported on two patients, brothers aged 28 and 31, whose attacks were quite controlled by the administration of potassium. The attacks were so irregular in their appearance that the potassium was no use prophylactically. The brothers had both been using potassium citrate on their own initiative for some time before they came under /

under the care of Herrington. The younger brother had taken up to 25 grammes in six hours without harm except mild catharsis. Sodium citrate was found to be quite ineffective.

It is probable that the action of potassium in familial periodic paralysis is at the myoneural junction, and that it acts by raising the excitability or the threshold value at the neuro-muscular junction. There must, however, be some other factor, as very low levels of the serum potassium can occur in individuals without causing paralysis.

Myotonia congenita and Dystrophia myotonica.

Thomsen himself, who was afflicted with the disease, recommended exercise in the treatment of myotonia congenita. The avoidance of cold and fatigue was counselled. There was no known specific treatment, and in the last edition (1937) of Price's Textbook of Medicine it is stated that the treatment of both myotonia congenita and dystrophia myotonica is entirely unavailing.

Claims were made, however, for several drugs. Soma Weiss and Foster Kennedy (1924) reduced the myotonia in a patient by giving atropine, which was even /

even more effective after previous sensitisation by thyroid. Their patient had an abnormally slow pulse and was a chronic sufferer from spastic constipation, indicating an abnormal increase in the activity of the parasympathetic nervous system. They attributed the success of atropine to its action as a parasympathetic depressant.

Pamboukis (1930) obtained relief in some cases by posterior pituitary gland, calcium chloride and acetosalicylic acid.

Lindsley and Curnen (1936), in an electromyographic study of myotonia obtained reduction in the amount and duration of the after contraction following the giving of calcium chloride and calcium gluconate.

Exactly sixty years after Thomsen had given his original description of myotonia congenita Alexander Wolf (1936) published his first report of the remarkable specific effect of quinine in relieving myotonia: three patients had myotonia congenita and one had myotonia dystrophica. Wolf tried all the remedies just mentioned on his patients, but found none of them effective in reducing the myotonia.

Various /

Various stimulants and depressants of the autonomic system were also tested but proved to be no use. The action of several alkaloids was then tried, and much the most remarkable effect was found with quinine. Wolf found that 10 grains of quinine dihydrochloride given intravenously acted in ten minutes, the effect lasting for from fifteen to twenty-four hours. Quinine hydrochloride grains 5-10 twice daily or thrice daily was found to be an adequate maintenance dose.

These observations on the value of quinine in myotonia were further established by Foster Kennedy and Wolf (1937) on four patients with dystrophia myotonica, by Smith (1937) on three siblings with myotonia congenita, by Laruelle, Massion-Verniory and Moldaver (1937) on one individual with dystrophia myotonica, by Kolb, Harvey and Whitehill (1938) on eight persons with dystrophia myotonica and one with myotonia congenita, and by Foster Kennedy and Wolf (1938) and Poncher and Wade (1938) on other myotonic individuals. So far as I am aware there have not yet been any reports in Britain on the value of quinine in myotonia, and it is part of my thesis to report my observations on three patients.

It /

It is not known how quinine acts in myotonia. Wolf's discovery was practically accidental and he gave no rationale. Foster Kennedy and Wolf (1937) suggested that quinine acted through inhibition of acetylcholine at the myoneural junction. This explanation has not been experimentally demonstrated, nor has it been conclusively proved that the disturbance in myotonia occurs at the myoneural junction. These points are discussed more fully later after a description has been given of my own experiments and observations.

As I have pointed out, however, it appears to be almost certain that the action of prostigmin in myasthenia gravis is at the myoneural junction. The clinical contrast between myotonia and myasthenia has been clearly shown by Foster Kennedy and Wolf (1937), who found with their patients that prostigmin exaggerated myotonia and quinine exaggerated myasthenia. These observations have been confirmed by Harvey and Whitehill (1937), who pointed out the usefulness of quinine as a diagnostic agent in myasthenia of slight degree, quinine increasing the symptoms to such a degree that the improvement following /

following the injection of prostigmin was easily recognised. Dr. W.R. Russell (1936) had no difficulty in demonstrating that 1.25 mgm. of prostigmin made myotonia definitely worse. Poncher and Wade (1938) also showed that prostigmin exaggerated myotonia. These results are, at any rate, suggestive that the action of quinine is at the myoneural junction.

As I have mentioned before, it is probable that potassium in relieving the paralysis of familial periodic paralysis acts at the myoneural junction. It is known that potassium improves the condition of myasthenia (Laurent and Walther, 1935). Furthermore, Dr. W.R. Russell (1936) has shown that potassium chloride or potassium citrate given by mouth makes myotonics worse within half an hour. I have myself confirmed this observation (see page 85). It seems likely, therefore, that potassium acts at the myoneural junction in myotonia as well as in myasthenia gravis and familial periodic paralysis. If giving potassium makes myotonia worse it might be possible to explain the action of quinine by examination of the blood of myotonics for serum potassium after the administration of quinine, the hypothesis being that an improvement in the clinical condition might be accompanied /

85

accompanied by a fall in the serum potassium.

Furthermore, Aitken, Allott, Castleden and Alker (1937) were able to induce attacks of paralysis in their patient with familial periodic paralysis by artificially lowering the level of the serum pottasium by giving insulin and glucose. On the analogy that potassium makes myotonia worse it seemed worth while to investigate the effect of insulin and glucose on myotonia, the assumption being that the clinical condition might improve.

The observation that alcohol improves myotonia (Russell, 1936) has been confirmed (Foster Kennedy and Wolf, 1938). My observations on the effect of beer on two myotonic individuals are reported and discussed and, at the same time, the serum potassium was examined.

It is known that extract of the suprarenal cortex lowers the serum potassium level. I have been able to try the effect of a small dose of Cortin (Organon laboratories) on myotonia and to examine the serum potassium level before and after the drug had been given.

The effect of insulin and glucose on the serum potassium of six individuals has been investigated and discussed.

I also hoped to make some clinical and experimental observations on a patient with familial periodic paralysis, but, as the patient refused to enter hospital for observation, the attempt had to be abandoned.

PRACTICAL PROCEDURES.

Technique of Collection of Samples of Blood.

Blood was obtained in each case by puncture of the median cubital vein on the flexor surface of the elbow joint, the vein being rendered prominent by a rubber tube wound round the upper arm in the form of a tourniquet. The skin surface was sterilised with methylated ether which was allowed to evaporate before the puncture was made. Venous blood was drawn off into a 10 c.c. Record syringe through a steel hypodermic needle of suitable bore, and was immediately transferred to a clean sterile test tube, which had been previously flushed out with distilled water and allowed to dry. The blood was allowed to clot, no oxalate or other anti-coagulant being added.

It was imperative to avoid any trace of potassium which might contaminate the syringe, needle or test tube; and also to avoid any trace of spirit or even distilled water which might cause some lysis of the red corpuscles and possibly disturb the relation of serum potassium to corpuscle potassium. Since about 95 per cent of the potassium in the blood is contained in the corpuscles, it is obvious that only a slight degree /

degree of haemolysis might cause a considerable rise in the level of the serum potassium. The syringe and needle were, therefore, thoroughly cleansed to avoid all traces of spirit, and on each occasion before use they were sterilised by boiling in distilled water, and then allowed to dry.

Each sample of blood was allowed to clot in the test tube for from half to one hour. The clot was then loosened from the side of the test tube by a glass rod, which had been drawn out to a fine taper, and which was rinsed with distilled water and dried each time before use. Within one hour of being obtained each sample was centrifuged for ten minutes at a constant speed. By a 2 ccm. pipette two ccm. of serum were drawn off immediately after spinning and were transferred to a wide bore Pyrex test tube for the first stage of the estimation of the serum potassium.

By separating the serum from the corpuscles every time within seventy-five minutes, and by carefully avoiding any haemolytic agent in the syringe or needle, I think I have avoided any possible loss of potassium from the corpuscles to the serum. Although the work of Crabtree and Maizels(1938) shows there is little danger from that point, I thought it advisable to centrifuge each specimen for the same length /

length of time (ten minutes) at a constant speed in order to avoid any possible error, due to shift of potassium from corpuscle to serum, being introduced by a variation in the length of spinning time.

Method of estimation of serum potassium.

The platinic chloride micro-titration method as described by Shohl and Bennett (1928) is used with slight modifications. This is the method used for routine estimations of serum potassium in the biochemical laboratories of the Royal Infirmary, Edinburgh. My own estimations were, however, all entirely carried out by myself, several weeks being spent in acquiring the technique. According to Peters and van Slyke (1932) "the accuracy of the Shohl and Bennett method is such that 0.1 mg. of potassium (the amount in 0.5 ccm. of serum) can usually be determined with an error within ± 4 per cent, and 0.4 mg. with an error within ± 2 per cent." As my estimations were all made with 2 ccm. of serum, reduced to four fifths of this value during the course of the procedure, the error was within ± 3 per cent and probably not much over ± 2 per cent.

Reagents /

Reagents

Sulphuric acid, approximately 4N.

Hydrogen peroxide 30% (Perhydrol, Merck).

Hydrochloric acid, approximately 1N.

Chloroplatinic acid containing 10 per cent of potassium: 26.5 grammes of chloroplatinic acid $H_2PtCl_6.6H_2O$ dissolved in water and diluted to 100 c.cm.

Absolute alcohol, redistilled over lime.

Absolute alcohol, redistilled over lime and saturated with a small quantity of the salt at intervals for several days.

Potassium chloride, 10 per cent, saturated with potassium chloroplatinate in the same manner.

Potassium iodide 2N.

Special solution for volumetric determination. Sodium thiosulphate 0.01N standardised daily with $\frac{N}{100}$ potassium bi-iodate.

To the 2 c.cm. of serum in the large Pyrex test tube add approximately 2 c.cm. of 4N sulphuric acid. The sample is then ready for "ashing."

It is evaporated on a steam bath for four to six hours. To the residue add two or three drops of Perhydrol. /

Perhydrol. The mixture is then brought to the boil on a Bunsen burner, great care being taken to avoid spluttering, and oxidation goes on until the hydrogen peroxide is used up. Allow it to cool so that more Perhydrol can be added without a violent reaction. Bring to the boil again very carefully. This process is repeated many times until a clear colourless solution is obtained when sulphuric acid fumes are escaping: it will usually take about three quarters of an hour. Care should be taken to see that all the hydrogen peroxide has been expelled before going on to the next stage.

The sample is then transferred with the help of some distilled water to a small platinum crucible. The crucible must be thoroughly cleaned beforehand by boiling with a few drops of concentrated hydrochloric acid and then rinsing with distilled water. For the transference a method found useful is to add exactly 5 c.cm. of distilled water to the residue in the Pyrex test tube, warm to just below boiling point, cool rapidly under cold water running from a tap, and then to remove exactly 4 c.cm. to the platinum crucible. It is at this stage that the sample is reduced /

reduced to four-fifths of its original value.

The platinum crucible is then heated over a steam bath, the water in the 4 c.cm. being thus evaporated. The last of the sulphuric acid is got rid of by heating the crucible very carefully over a small Bunsen flame. The greatest care is necessary at this stage in order to avoid spitting. The material is finally dried thoroughly by heating to redness. All organic matter has now been removed.

With a rubber tipped glass rod and some distilled water, wash out the ash residue from the platinum crucible into a glass evaporating bowl. Evaporate to dryness on a steam bath.

Now add two drops of normal hydrochloric acid to dissolve the residue, using a plain glass rod to aid the solution. Then add 5 c.cm. of absolute alcohol (redistilled over lime). Leave for twenty minutes to obtain full precipitation of the double salt potassium platinic chloride.

Transfer the precipitate to a Shohl micro filter by washing over with alcohol saturated with potassium chloroplatinate. The excess of platinum is filtered off by suction and saved for recovery. The precipitate and filter are then washed four or five times /

times with alcohol saturated with potassium chloroplatinate. Some contaminating salts, which are precipitated with the chloroplatinate in alcohol, are washed out with three or four portions of the solution of 10 per cent potassium chloride saturated with potassium chloroplatinate.

The funnel containing the precipitate is now removed from the filtering apparatus and inverted over a suitable clean wide test tube. The asbestos and the precipitate are then pushed out into the test tube by a small glass rod inserted down the stem of the funnel. The funnel is then turned right end up and its sides and the glass rod are washed with about 2 c.cm. of hot distilled water to transfer all traces of precipitate to the test tube.

Then add 1 c.cm. of potassium iodide 2N solution, and heat the mixture in a water bath at 65 degrees Centigrade for fifteen minutes. The solution is immediately titrated, while still warm, with the 0.01N sodium thiosulphate delivered from a micro-burette with 0.01 c.cm. divisions. The end point is when the colour in changing from red to canary yellow first loses all traces of red. During the titration the test tube should be shaken.

It /

It will be understood that this is a somewhat complicated and certainly a most tedious technique which requires considerable practice before facility and accuracy are acquired. I spent about one month in learning the method and gaining sufficient dexterity to make my estimations absolutely reliable. Blank determinations were also carried out using distilled water as the unknown solution. Great care must be taken throughout the procedure to avoid contamination with extraneous potassium. Pipettes and test tubes were made scrupulously clean, and were always rinsed thoroughly with distilled water.

The quantitative determination depends upon the conversion of potassium chloroplatinate to potassium iodoplatinate by the addition of potassium iodide. The iodoplatinate in solution forms a deep rich wine colour. In neutral solution the potassium iodoplatinate is readily reduced by sodium thiosulphate. Owing to the lemon yellow colour of the reduced salt in solution, the iodine salt is a self indicator.

Method /

Method of Calculation.

The equivalent weight of potassium is 39.1

Normal solution contains 39.1 gms. potassium per litre.

$\frac{N}{100}$ " " 0.391 " " " "

$\frac{N}{100}$ " " 0.391 mg. " " c.cm.

One c.cm. $\frac{N}{100}$ sodium thiosulphate = 0.391 mg. potassium.

Let A and B represent amount in c.cm. of $\frac{N}{100}$ sodium thiosulphate used for the titration of the unknown solution and the blank respectively, and N the normality of the $\frac{N}{100}$ sodium thiosulphate.

Then $\frac{0.391(A-B) \times 100 \times 5 \times N}{8}$ = mg. of potassium per 100 c.cm. of serum because $\frac{4}{5}$ of 2 c.cm. or $\frac{8}{5}$ c.cm. was the volume of the material represented by the sample analysed.

Therefore mg. of potassium per 100 c.cm. of serum = $\frac{N \times 39.1 (A-B) \times 5}{8}$

= N x 24.4375 (A - B)

= N x 24.44 (A - B)

The normality of the $\frac{N}{100}$ sodium thiosulphate varied from $\frac{2}{1.72}$ to $\frac{2}{1.78}$.

Having explained the method of calculation of the potassium content in mg. per cent of each sample examined, I do not propose to give the calculations step by step for each sample. I will only give final figures /

figures for the potassium content in mg. per cent.

The comparatively little work done on variations in the serum potassium has been mainly on animals. The probable reason for so little work is the inherent difficulty of the determinations. Great care has to be taken at each stage of the estimation, and, as one is working with less than half a milligram in each same sample, serious errors may result from slight loss or contamination.

A further difficulty is the length of time required for each estimation. Even after full practice, I found that the most I could do in one week working about ten hours a day and alone, was to withdraw one dozen samples of blood and estimate the potassium in them. In parenthesis I might add here that before I worked in a biochemical laboratory I had no idea of the length of time required to do some of the routine procedures, and I feel sure that if clinicians realised this they would not request so much unnecessary data.

Another difficulty in connection with work on the serum potassium is that there is rather a wide variation in the normal level, which is usually given as /

as 18(±3)mg. per cent. There is a variation of 33 per cent. round the normal mean. Therefore only gross variations from the normal would appear to be of any significance. Further, as may be seen from my figures (page 57) the serum potassium may vary as much as from 13.7 mg. per cent to 21.9 mg. per cent in less than two hours, so that isolated observations are not of much use.

Again, potassium is present in all the tissues of the body, and there is no recognised storehouse for potassium. Recent work by Da Silva (1936) suggested, however, that the liver may store potassium in some peculiar manner, and this has been confirmed by Marenzi and Gerschman (1937) and also by Houssay, Marenzi and Gerschman (1937) who showed, after the extirpation of various internal organs of the dog, that the intact liver was the one organ essential to produce a rise in serum potassium following injection of adrenalin, ephedrine and other drugs.

THE LEVEL OF THE SERUM POTASSIUM AFTER INGESTION OF 50.0g. OF GLUCOSE AND LAEVULOSE.

The level of the serum potassium after ingestion of 50.0g. of glucose was studied in three individuals, a man of twenty-five with myotonia, a woman of fifty-eight with moderately severe diabetes and a woman of twenty-three with disseminated sclerosis. In a fourth subject, a boy of ten years with hepato-lenticular degeneration (Wilson's disease) 50.0g. of laevulose were given instead of the glucose. In these persons the first samples were taken in the morning after overnight fasting. Further samples of blood were taken at half-hourly intervals for two hours after the ingestion of the carbohydrate. Samples were also taken for blood sugar estimation at each of these times, and in the case of the boy with Wilson's disease the blood laevulose was also estimated. (I am grateful for the figures of these estimations to Mr. Thompson and Mr. Whitaker of the Biochemical Department of the Royal Infirmary, Edinburgh.)

(1). /

(1).

W.W. Age, 25. Myotonia. March 21st, 1938.

Time.	Serum potass. in mg. per 100 c.cm.	Blood sugar in mg. per 100 c.cm.
zero	17.7	90
½ hour	13.76	183
1 hour	16.57	160
1½ hours	15.7	129
2 hours	21.9	92

50.0g glucose given at zero.

Note. During the time of these observations there was no change in the clinical state of myotonia.
The blood sugar curve is above normal.

(2).

Mrs. B. Age, 58. Diabetes. Not on insulin on day of test, but had been having 40 units a day.

February 23rd, 1938.

Time	Serum potass. in mg. per 100 c.cm.	Blood sugar in mg. per 100 c.cm.
zero	20.6	280
½ hour	20.2	395
1 hour	16.0	368
1½ hours	17.4	340
2 hours	20.2	297

50.0g glucose given at zero.

Note. The drop in serum potassium is delayed until sugar begins to disappear from the blood.

(3).

Mrs. P. Age, 23. Disseminated sclerosis.

April 5th, 1938.

Time	Serum potass. in mg. per 100 c.cm.	Blood sugar in mg. per 100 c.cm.
zero	15.7	102
½ hour	16.0	131
1 hour	14.6	116
1½ hours	14.6	99
2 hours	15.7	102

50.0g glucose given at zero.

(4).

J.K. Age, 12. Wilson's disease. March 10th, 1938.

Time	Serum potass.	Total blood sugar.	Blood laevulose.
zero	16.48	107	2
½ hour	14.78	147	20
1 hour	10.8	162	15
1½ hours	15.9	152	8
2 hours	14.78	146	7

50.0g. laevulose given at zero.

The figures given in all cases represent mg. per 100 c.cm. serum or blood. Sugar estimation method - Hagedom and Jensen. Laevulose estimation method - Diphenylamine.

Note. The laevulose test shows a borderline disturbance of liver function.

In all four persons there was a definite fall in the level of the serum potassium after the ingestion of the carbohydrate, and in each case the lowest level was reached within one hour of the ingestion. At the end of two hours the serum potassium level was equal to, or higher than, the initial level in all except the boy with Wilson's disease. In his case, not only did the serum potassium fall to a very low level (10.8 mg. per cent), but, at the end of two hours, the initial level had not been regained. This delay in the return of the serum potassium to the normal level is of interest in connection with the possibility of the liver being the storehouse for potassium. Clinically this boy had cirrhosis of the liver and the laevulose test showed a borderline disturbance of function. Was the liver unable to respond to the low level of serum potassium?

THE LEVEL OF THE SERUM POTASSIUM AFTER INJECTION OF INSULIN.

The serum potassium level was studied in two subjects after the injection of 10 units and 12 units of insulin respectively. One was a male diabetic, twenty-seven years old, who was in hospital for adjustment of his dose of insulin. He received his usual morning dose of insulin (12 units) and half an hour later his usual breakfast. The other was a healthy youth of seventeen who had previously fasted for ten hours.

(5).

D.V. Age, 27. Diabetes, April 4th, 1938.

Time	Serum potassium in mg. per 100 c.cm.	Blood sugar in mg. per 100 c.cm.
zero	21.3	121
½ hour	19.7	170
1 hour	18.8	149
1½ hour	15.7	126
2 hours	17.1	120

12 units of insulin given at zero. At ½ hour he ate his breakfast, the gluose value of which was 35g.

(6). /

(6).

J.M.A.G. Age, 17. Normal. May 11th, 1938.

Time	Serum potass. in mg. per 100 c.cm.	Blood sugar in mg. per 100 c.cm.
zero	18.17	86
½ hour	17.6	84
1 hour	16.18	76
1½ hours	18.46	80
2 hours	18.46	89

10 units of insulin given at zero.

It will be seen from these figures that the fall in the level of the serum potassium was much more pronounced in the diabetic. He received a very slightly larger dose of insulin, but the factor causing the great fall was, in all probability, the accompanying meal. These findings agree with the observation of Aitken, Allott, Castleden and Walker (1937), that insulin and glucose, separately or together, produce a fall in the level of the serum potassium, but that the fall after glucose and insulin together is greater than the fall after insulin or glucose alone. In the case of the diabetic the meal takes the place of the glucose.

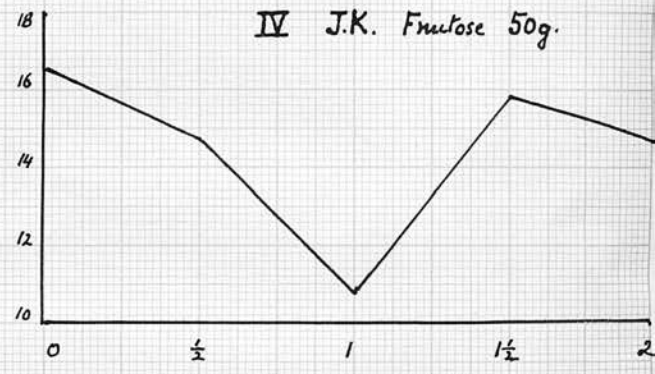
In /

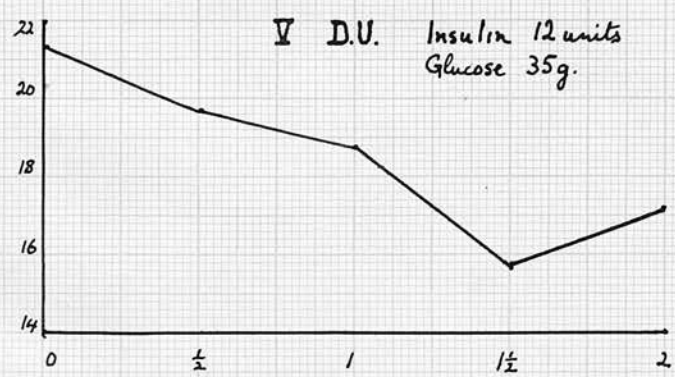
In the young man (Table 6) the serum potassium reached its lowest level one hour after the insulin injection, as it did in the four subjects who received 50.0g. of glucose. In the diabetic (Table 5), however, the lowest level was reached slightly later. My interpretation is that in his case the fall was initiated by the insulin but was accentuated by the absorption of the carbohydrate in the meal.

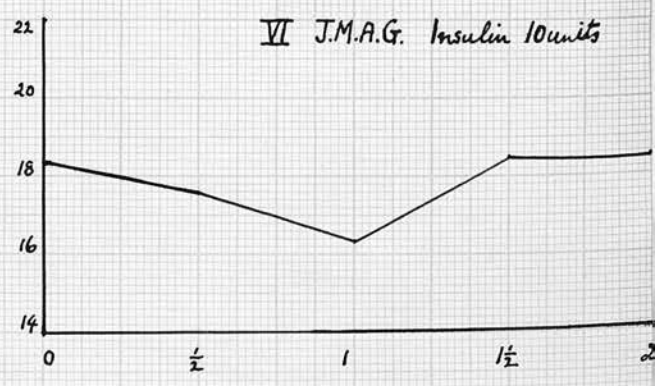
COMMENTARY ON THE SIX SERUM POTASSIUM CURVES.

It will be seen that in all except the man (Table 6) who received insulin alone the level of the blood sugar rose as the serum potassium fell, and also that the rise in the blood sugar slightly preceded the fall in the serum potassium.

In three persons (Tables 1,2 and 3) the blood sugar returned to its initial level while the serum potassium returned to or even exceeded its initial level. In the boy with Wilson's disease (Table 4), however, at the end of the two hour period the total blood sugar had not fallen to the initial level, and the serum potassium was still below its initial level. This probably indicates that, while the metabolism of sugar is still preceding, the serum potassium /







ORDINATES = SERUM POTASSIUM IN MG. PER CENT.

ABSCISSAE = TIME IN HOURS AFTER CARBOHYDRATE OR INSULIN.

potassium level remains low. There is also the additional factor, as mentioned before, that the cirrhotic liver may have been either deficient in potassium or slow in restoring the normal level of serum potassium. The laevulose test showed that it was on the borderline of abnormality, and in any case he definitely had cirrhosis of the liver. It is possible that the functional capacity of the liver may be greatly impaired before any abnormality is detected by the laevulose test (Stewart, Scarborough and Davidson, 1938). Da Silva (1936) has shown that after injection of adrenalin potassium is mobilised from the liver. This does not, of course, necessarily mean that during the depression of the serum potassium after ingestion of a sugar the potassium disappears from the serum to the liver, to return from the liver to the serum as its level rises in the serum. Actually, as I shall show later, it is probable that the potassium is used up temporarily during an intermediate stage of sugar metabolism. My conclusion is that the prolonged depression of the serum potassium in Table 4 in comparison /

comparison with Tables 1, 2 and 3 is due to the metabolic disposal of the fructose ingested by a boy with a cirrhotic liver being greatly delayed.

In the man (Table 6) who received insulin alone, there was a slight fall in the blood sugar level while the serum potassium fell. It cannot be, therefore, that the serum potassium falls because the blood sugar rises. It seems that serum potassium falls as sugar is withdrawn from the blood. It falls after insulin injection because this removes sugar from the blood; and it falls after ingested sugar or carbohydrate because sugar is withdrawn from the blood, under endogenous insulin mechanism, to make room for the ingested carbohydrate which has temporarily raised the level of the blood sugar. The assumption is that potassium is concerned in some way with the metabolism of the glycogen which is being formed from the sugar withdrawn from the blood.

Harrop and Benedict (1922), in publishing a preliminary note, were the first to call attention to the effect of insulin upon the inorganic phosphate and potassium of the blood.

Briggs, Koeschig, Doisy and Webber (1923) found that /

that injection of insulin into dogs caused a depression of the serum potassium and inorganic phosphate: they also found a decrease in the bicarbonate and a lowering of the pH value. Simultaneously there was an increase in the blood lactic acid which was apparently formed from glucose under the influence of insulin. No change was found in the level of the sodium, calcium, magnesium or chlorides. They were unable to interpret their findings in connection with potassium. According to them there was a loss from the blood cells as well as from the plasma.

Harrop and Benedict (1924), examining the serum inorganic phosphate and potassium of five human diabetics and one normal person after the injection of insulin, found in all cases a fall in the level of both. They also made experiments on five rabbits, A, B, C, D and E. A and B were given intravenous insulin and there was a fall in the phosphate and potassium. There was no fall after intravenous saline in C. In D and E they found a marked rise in the phosphate and potassium after strychnine convulsions. They suggested that by the convulsions glycogen /

glycogen was broken down liberating lactic and phosphoric acid and potassium.

In further experiments Harrop and Benedict (1924) gave a constant diet to a moderately severe diabetic who had not received insulin. After a preliminary period he was given insulin on certain days. On the days on which insulin was given the excretion of urinary phosphate and potassium was reduced during the hours in which insulin was actively influencing metabolism. The release of this retained phosphate and potassium, with a great increase in the urinary excretion of both of them, occurred during the following night when the effect of insulin was ended. The greatly increased night excretion, following each of the insulin days, was in sharp contrast to the much smaller night excretion of the control day. These variations in urinary excretion corresponded in general with like variations in the serum concentration of phosphate and potassium. When the serum concentration was low, the urinary excretion was also low.

Harrop and Benedict (1924) also found an increased concentration of phosphate in the muscle tissues following the injection of insulin, and a decrease of serum phosphate with a rise of blood sugar following the ingestion of 200g. of glucose in three normal individuals (due to stimulation of the pancreas to pour out insulin). The time of the lowest depression of phosphate did not coincide with, but followed, that of the highest level of blood sugar concentration. This accords with my finding in the case of potassium in the four individuals who took 50g. of carbohydrate, in that in two of them, (Tables 2 and 3) the lowest depression of serum potassium followed the highest level of blood sugar concentration and in the other two (Tables 1 and 4) they coincided.

These experiments of Harrop and Benedict agree with their hypothesis that an intermediary phosphate compound is formed during the conversion of glucose into muscle glycogen or during the oxidation of glucose. They suggested that there is a shift of the available phosphates and potassium from the blood serum into the muscle tissues while glycogen is being formed. Consequently there is at one and the same time /

time a lowering of the serum concentration of phosphate and potassium, a drop in their urinary excretion and an increase in their concentration in the muscles; all of which were demonstrated in their experiments except an increase of potassium in the muscles. They thought that the potassium is united in some way with the intermediary carbohydrate phosphate compound, and that the fall in serum potassium is due to the production of potassium hexose phosphate as a step in the mobilisation and utilization of carbohydrate.

Kerr (1928) determined the phosphorus and potassium content of the blood serum of dogs following over dosage with insulin. He found the serum concentration of potassium greatly decreased after insulin, and at the same time no change in the concentration of potassium in the corpuscles. From a further series of experiments on dogs after pancreatectomy he concluded that the potassium content of corpuscles is not affected directly by the presence or absence of insulin. His evidence indicates without question that the potassium which disappears from the serum does not enter the corpuscles. In my opinion his findings do not invalidate /

invalidate but support Harrop and Benedict's interpretation of the role of potassium in the metabolism of glucose.

My conclusion, therefore, is that the temporary fall in the level of serum potassium after ingestion of carbohydrate or injection of insulin is due to potassium being necessary for the formation of the intermediary carbohydrate phosphate compound in the metabolism of glucose to glycogen. The serum potassium level rises again as the potassium is released when the glycogen is formed.

The clinical significance of the fall in the level of the serum potassium in familial periodic paralysis has been amply demonstrated by Aitken, Allott, Castleden and Walker (1937), and the significance of food as a factor in precipitating paralytic attacks has been noted by Mitchell, Flexner and Edsall (1902), Gardner (1912), Zabriskie and Frantz (1932), Biemond and Daniels (1934) and others, and is well known.

A raised serum potassium level is a well known feature of Addison's disease (of the adrenal glands). Apart from familial periodic paralysis and Addison's disease /

disease I do not know of any condition in which it is known that a change of the serum potassium level has any clinical significance. For reasons which I will state, however, I think that the serum potassium level may be important in several conditions, and I propose now to put forward my hypothesis in connection with diabetes.

THE SERUM POTASSIUM AND DIABETES.

Kerr (1928) mentioned a diabetic patient who was given insulin for six days: on the seventh day, two and a quarter hours after the injection of forty units of insulin, the serum potassium level was found to have fallen to 7.2 mg. per cent. after being 17.0 mg. per cent at the beginning of the period of observation. Harrop and Benedict (1924) gave the serum potassium figures for a patient who died in diabetic coma. This individual received 135 units of insulin in thirty hours and, during this time, the serum potassium level dropped from 14.3 mg. per cent to 10.5 mg. per cent ten hours before death. Nine hours before death (one hour after the last serum potassium observation) a further twenty units of insulin were given. In the two diabetic patients /

patients (Tables 2 and 5) whose serum potassium level after insulin injection was investigated by myself, the fall was from 20.6 and 21.3 mg. per cent to 16.0 and 15.7 mg. per cent respectively. These figures show that insulin produces a considerable fall in the level of the serum potassium in diabetics and, with glucose in addition, the fall must be even greater.

It is well known that some diabetics, who have recovered from coma with proper treatment by insulin, glucose and alkalis and who appear to be well on the road to recovery, die fairly suddenly from myocardial failure. Lande (1933) in discussing the cause of death in diabetes reported on ten persons who failed to recover from uncomplicated diabetic coma. Two of them regained consciousness: one received 600 units of insulin in eight hours, the blood sugar level falling to normal, and consciousness returning before the end came with hyperpyrexia; the other, after receiving 175g. of glucose and 140 units of insulin in twenty-four hours, regained consciousness and then suddenly collapsed on the third day. The eight other patients died from "vasomotor collapse" or hyperpyrexia. Lande, in commenting on these deaths, said "I believe that there are factors of great importance other than the control of carbohydrate /

carbohydrate metabolism and the overcoming of ketosis by insulin, and that an appreciable coma mortality is inevitable in a general hospital even with adequate treatment."

Ralli and Waterhouse (1934) reported eight deaths in diabetic coma, four of which were due to myocardial failure. All their patients were given infusions of saline with glucose (50 g. per 1000 c.cm.) and an initial dose of 40 units of insulin followed by 20 units every half hour. Post-mortem histological changes were found in three of the four persons who died from cardiac failure. It is here appropriate for my purpose to quote Lawrence (1930) who wrote: "Many physicians must have had the disappointing experience of losing a certain proportion of cases of diabetic coma even since the introduction of insulin. From all countries records and statistics show a varying number of patients who die in spite of energetic treatment with insulin."

Temporary dilatation of the heart is a well recognised feature of the paralytic attacks of familial periodic paralysis. Singer and Goodbody (1901) and Bender (1936) quote Westphal (1885) as the first to observe this dilatation of the heart, and /

and they further state that Goldflam (1891) and Mitchell (1899) during attacks of periodic paralysis found systolic murmurs without enlargement of the area of cardiac dulness. Hirsch (1894) and Singer found enlargement of the area of cardiac dulness with some impurity of the first sound but no murmur. Singer concluded "from these observations it will be seen that the change consists in dilatation with or without definite regurgitation through the mitral valve." Dilatation of the heart has also been described by Holtzapple (1905) and Janota and Weber (1928). Holtzapple thought that death was due to cardiac dilatation in one of his patients who died during an attack of paralysis. Two deaths during attacks of paralysis were attributed by MacLachlan (1932) to respiratory failure during attacks of choking and coughing, but may well have been due to cardiac failure. Death during an attack owing to cardiac dilatation has been reported by Schmidt (1919) and Bender (1936). From what I have just said it will be realised that cardiac dilatation is common during attacks of periodic paralysis and that death from cardiac dilatation during an attack is by no means rare.

Now, /

Now, this death from cardiac dilatation during an attack of periodic paralysis must occur when the serum potassium level is low, and may possibly be actually due to the low serum potassium. In the energetic treatment of diabetic coma large quantities of glucose and insulin are given for many hours, and, as we have seen, this must inevitably lead to a very low level of serum potassium. Salines are usually also given, but these nearly always contain only the sodium ion and no potassium ion. Lawrence (1930) used double strength (1.8 per cent) sodium chloride solution. The marked diuresis of severe diabetes leads to great loss of sodium and potassium, but only the sodium is replaced, thus accentuating the relative disproportion between sodium and potassium already caused by repeated doses of insulin and glucose. It seems to me, therefore, that there is a very suggestive similarity between the deaths from cardiac dilatation in familial periodic paralysis and the deaths, unexplained or due to cardiac failure, in patients with uncomplicated diabetic coma who have received proper treatment. In both cases there is a very low serum potassium level at the time of death.

The /

The function of the frog's heart is dependent on the concentration of potassium in the fluid surrounding the cells and is, to a certain extent, independent of the amount of potassium within the cells (Clark, 1933). He further states:"The writer considers the following to be a fair summary of the evidence available. Straub was correct in his conclusion that, in many if not most cases, drugs outside a cell have an action quite different from the action of drugs that have entered a cell. The action of potassium ions is the most striking example of this fact, for the ratio of their concentration inside and outside of muscle-cells is about thirty to one. A fourfold increase or reduction of the outside concentration is, however, sufficient to paralyse the frog's heart." This evidence from the frog's heart supports my contention that death from cardiac failure in an attack of familial periodic paralysis, and in a properly treated case of uncomplicated diabetic coma, is due to a very low serum potassium concentration acting as in the case of the frog's heart.

The /

The hypothesis is conjectural but is worth investigation at some time. My practical suggestion is that potassium should always be included in the saline solution used during the treatment of collapse in diabetic coma. It can do no harm and it may save a life.

OBSERVATIONS ON MYOTONIA.

I was fortunate in being able to study three men with myotonia. One, who had three brothers also suffering from the same symptoms, had myotonia congenita (Thomsen's disease). In the case of the other two it was difficult to make an absolute diagnosis of myotonia congenita or dystrophia myotonica, a difficulty which I will discuss later. For present purposes it is enough to say that they all had typical myotonic symptoms.

Intravenous Quinine.

Wolf (1936) in his first report on the specific action of quinine in myotonia stated that he found clinical improvement after the intravenous administration of quinine. My patient, W.W., was given intravenous quinine, after previous oral testing for idiosyncrasy, on three separate occasions, but each time the clinical effect was disappointing. He was twice given 5gr. quinine bihydrochloride intravenously with no subjective or objective improvement.

On the third occasion he received 10gr. of quinine bihydrochloride intravenously. After 1½ hours there was a doubtful objective improvement as shown /

shown by examination of the eyelids. After 3¼ hours there was a definite diminution in the tone of the eyelids after closing them tightly, and the patient himself volunteered that he felt slightly better.

Some explanation is here necessary concerning the objective demonstration of clinical improvement in myotonia. In the patient W.W. improvement appeared first in the eyelids. Normally after tight closure of the eyelids he could not open them properly for nearly ten seconds: but after repeating the tight closure several times he could open and shut his eyelids like any normal person, and only after an interval of several minutes was there any return of the delay in relaxation. In W.W. it was found that twenty minutes after exercising the eyelids, the myotonia was just as marked as it had been before the exercise. Therefore, in using the myotonia of the eyelids as a test of the clinical condition after giving drugs, it was always found necessary to allow an interval of at least twenty minutes between each test. The same applies to myotonia in other parts of the body.

Apart from the fact that intravenous quinine is impracticable for daily treatment of myotonia and /

and in W.W.'s case had little effect, there were other features which made me decide that its use is unjustifiable. The injections were given slowly, taking one minute for the full dose of ten grains: during the injection of the ten grains W.W. perspired freely, huge beads of perspiration appearing on his forehead. His pulse became rapid, and he looked pale and felt faint, with a tingling sensation in his limbs. But his most disturbing sensation was a very hot feeling at the back of his throat, which was only present during the actual injection: this was so unpleasant that he asked that no further intravenous injections of quinine should be given to him.

Intravenous quinine was given to two normal subjects, a volunteer (J.C.T.) and myself, who both took quinine bihydrochloride grains 10 orally beforehand to exclude idiosyncrasy. J.C.T. had slight tinnitus and deafness but I felt no ill effects. We were both given quinine bihydrochloride gr. 10 intravenously.

During the injection of J.C.T. his face became flushed and the conjunctivae intensely congested. This /

This was followed in about half a minute by obvious pallor of the face with slight perspiration on the forehead. His pulse became rapid and feeble. Tingling in the extremities was felt during, and shortly after, the injection. Intense buzzing in the ears was followed by slight deafness lasting for twelve hours. He also felt the intense burning at the back of the throat that W.W. found so unpleasant. Slight faintness and mental confusion made it necessary for him to lie down for a few minutes after the injection. I myself also felt tingling in the limbs and a very unpleasant hot sensation in the throat during the injection: palpitation was probably due to anxiety. Because of these experiences I would confine the use of intravenous quinine to the emergency treatment of severe malaria.

Samples of blood for estimation of serum potassium were obtained from W.W., J.C.T. and myself immediately before the intravenous injections and at a varying interval afterwards. In all cases quinine bihydrochloride was used.

(7). /

(7).

W.W. Age, 25. Myotonia. March 7th, 1938.

Time	Serum potassium in mg. per cent.
11.45 a.m.	16.77
12.30 p.m. I.V. injection quinine gr. 5.	
1.30 p.m.	21.6

Note:- No clinical improvement. Fasting over three hours before the samples were taken.

(8).

W.W. Age, 25. Myotonia. March 8th, 1938.

Time	Serum potassium in mg. per cent.
11.50 a.m.	15.06
11.55 a.m. I.V. injection quinine gr. 10.	
3.15 p.m.	19.61

Note:- Slight clinical improvement at 3.15 p.m. Fasting over three hours before first sample. Ordinary meal at 12.45 p.m.

(9).

J.C.T. Age, 26. Normal. March 11th, 1938.

Time	Serum potassium in mg. per cent.
9.20 a.m.	15.9
9.25 a.m. /	

Time	Serum potass. in mg. per cent.
9.25 a.m. I.V. injection quinine gr. 10.	
9.45 a.m.	17.34
10.30 a.m.	16.48

Note:- Samples all taken after fasting over twelve hours.

(10).

G.M.G. Age, 33. Normal. March 11th, 1938.

Time	Serum potassium in mg. per cent.
9.40 a.m.	15.4
9.45 a.m. I.V. injection quinine gr. 10.	
9.50 a.m.	14.0
11.00 a.m.	14.3

Note:- Samples all taken after fasting for over twelve hours.

It will be noted that the serum potassium level in W.W. rose after both the gr. 5 and the gr. 10 doses, and in the latter case it had risen by approximately thirty per cent when clinical improvement first appeared. Therefore, although taking potassium salts may increase myotonia (Russell, 1936) and made W.W. worse (see page), clinical improvement /

improvement can take place with a rise in the level of the serum potassium.

In Tables 9 and 10 the serum potassium level was variable after the injections, being slightly higher in 9 and slightly lower in 10. From these figures it is not possible to make any statement about the effect, if any, of the intravenous injection of quinine upon the serum potassium level. Keys (1938) has shown that in man the intravenous injection of epinephrin (0.005 to 0.3 mg.) produces an immediate and marked fall in the level of the serum potassium, which returns to near normal in about twenty minutes and is generally above the pre-epinephrin level after forty to sixty minutes. One cannot, therefore, exclude the possibility that the level of the serum potassium after an intravenous injection of quinine may be influenced by excess secretion of adrenalin owing to anxiety. In my own case (Table 10) I was extremely anxious after watching the effect of the injection on J.C.T. Owing to the rather alarming symptoms further experiments with intravenous quinine were out of the question, and no definite deductions can be made from /

from the figures in Tables 7 to 10 as to the effect of the intravenous injection of quinine upon the serum potassium level

Oral Quinine.

The patient W.W. was given quinine bihydrochloride orally many times: the bihydrochloride was much more effective than the sulphate of quinine. The improvement after a single dose of quinine bihydrochloride lasted for at least ten hours and, on one occasion, for about seventeen hours. After a dose the myotonic reaction to the galvanic current disappeared first, later the reaction to mechanical percussion and, last of all, the myotonia on voluntary movement. After a single dose of bihydrochloride gr.15 W.W. felt better in about thirty minutes. After one hour there was usually no myotonia in the eyelids after tight closing, no difficulty in starting to walk, no myotonic reaction to mechanical percussion: but there was still some delay in relaxation after a tight hand grip; it usually took about two hours for all myotonia to disappear from the hand muscles.

It was found that quinine bihydrochloride gr.25 daily, divided into two or three doses, was adequate to /

to maintain complete freedom from myotonia. W.W. on this dose had no tinnitus or deafness.

Oral Potassium.

The effect of a dose of potassium salt was tested on the patient W.W. He was kept in bed and given potassium chloride gr.75 just after his mid-day meal. In one hour myotonia was definitely increased: after tight closing he was unable to open his eyelids for thirty seconds in contrast with the normal delay of between five and ten seconds.

After an hour and a half his whole body was stiff and he was unable to turn over in bed; his neck, which normally was not in the least stiff, could only be bent with difficulty. Immediately after tight shutting of the eyelids he was quite unable, in spite of intense effort with auxiliary muscles such as the occipito-frontalis, to produce the small slit aperture between the upper and lower lids which normally appeared at once.

About two hours after taking the potassium salt his condition was so uncomfortable that he asked for quinine to relieve him. He was immediately given quinine bihydrochloride gr.10 by mouth; in three quarters of an hour he was so much better that he could /

could shut and open his eyelids without any delay, and there was no myotonia on tight gripping with either hand.

This increased myotonia after potassium chloride agrees with the observations of Dr. W. Ritchie Russell (1936). On the other hand, Poncher and Wade (1938) gave potassium acetate 1g. every half hour for six doses (a total of 6g.) to a patient with myotonia congenita without any effect whatsoever. They were apparently looking for clinical improvement after potassium as they quoted Pansini as having suggested potassium therapeutically in myotonia because potassium removes veratrine contractures which resemble the myotonic spasm. Kolb, Harvey and Whitehill (1938) gave up to 12 c.cm. t.i.d. of a 25 per cent solution of potassium chloride without improvement: there is no mention that the myotonia became worse.

Having established that W.W. improved after quinine and became much worse after a potassium salt, I took samples of blood for serum potassium estimation to determine if any correlation could be found between the degree of myotonia and the serum potassium content of the blood.

Serum potassium after Oral Quinine and Potassium.

(11).

W.W. Age, 25. Myotonia. March 16th, 1938.

Time	Serum potassium in mg. per cent.
9.45 a.m. (Quinine gr.15 by mouth)	15.35
11 a.m.	20.75
12.30 p.m.	13.93

Note:- Slight improvement in half an hour, quite definite one hour after taking quinine.

At 11 a.m. only slight myotonia in eyelids, and on gripping.

At 11.15 a.m. walked round ward easily. Going upstairs was slightly stiff at sixth step (normally stiff at second or third step). Pace upstairs increased to normal again, as soon as sixth step was overcome.

At 12.15 p.m.- No myotonia in eyelids or on hand gripping. Stiff on fourth step on going upstairs, but after walking briskly round the ward he reached the sixth step without difficulty, where he again was slightly stiff.

The effect of the quinine lasted for about seventeen hours.

(12). /

(12).

W.W. Myotonia. March 18th, 1938.

Time	Serum potassium in mg. per cent.
1.15 p.m.	18.47
1.30 p.m. - took potass. chloride gr.75.	
2.30 p.m.	19.61
3.45 p.m. - took quinine gr.10 orally.	18.4
5.0 p.m.	15.35

Note:- At 2.30 p.m. increased stiffness. At 3 p.m. very stiff, neck bent with difficulty and scarcely able to move in bed. Marked myotonia in eyelids.

At 3.45 p.m. took quinine gr.10 orally, with complete relief of myotonia in about forty-five minutes.

(13).

W.W. Myotonia. Fasting 12 hours. May 4th, 1938.

Time	Serum potassium in mg. per cent.
9.15 a.m. - took quinine gr.15.	25.57
10 a.m.	23.04
11 a.m.	16.8
12 noon	16.8

Note:- Felt better in $\frac{1}{2}$ hour after quinine. No myotonia in eyelids in $\frac{3}{4}$ hour. Effect of quinine lasted for about nine hours.

It /

It will be seen from the figures given that the absolute level of the serum potassium had no relation to the state of myotonia of the subject. In Table 11 the serum potassium rose from 15.3 mg. per cent to 20.7 mg. per cent in just over an hour after the quinine, yet the patient improved considerably during this time. In Table 12 the serum potassium rose from 18.47 mg. per cent to 19.6 mg. per cent in just over an hour, yet the myotonia was much worse because of the dose of potassium.

It may seem curious that in Table 11 there was a rise from 15.3 to 20.7 mg. per cent without a dose of potassium, yet in Table 12 there was a rise of only just over 1 mg. per cent in spite of a fairly large dose of a potassium salt. According to Sollman (1936) the excretory capacity for potassium ions is usually much greater than the rate of absorption from the alimentary canal. "Oral administration is, therefore, effective only if very large doses are given." The effect of this dose of potassium chloride (gr.75) would seen to have been partly diuretic: it would seem to have been partly absorbed by the tissues, causing an increase of myotonia, any great rise in the level of the serum potassium /

potassium being prevented by diuresis. There is also to be taken into account the fact that he had his midday meal just before taking the dose of potassium chloride. This meal would probably reduce to some extent the expected rise in the serum potassium. These are the only explanations I can give for the figures in Table 12.

It will be noted in Tables 11, 12 and 13 that there is a range from 15.35 to 25.57 mg. per cent for the figures for the initial samples in each case: yet, as far as could be judged, there was no difference in the myotonia. This is yet another demonstration that, in spite of potassium making myotonia worse, there is no correspondence between the level of the serum potassium and the degree of myotonia. It is worth noting that the high figure of 25.57 was obtained after an all-night fast. Another point is that, at the period of maximum clinical improvement after quinine, the serum potassium was in all cases at a level lower than before the administration of quinine. This is in accordance with a possible hypothesis that quinine acts by withdrawal of potassium from the tissues, changing the intra- and extra-cellular ratio, but, of course, it in no way proves it.

Some /

Some support for the impression that quinine has some effect on the level of the serum potassium is afforded by the following Tables (14 and 15) showing the figures for serum potassium after two doses of potassium chloride gr.75, the second dose being followed in one hour by quinine bihydrochloride gr.10. The samples were taken from the same man who, on both occasions, had had an early light breakfast and had fasted for three hours before the samples were taken.

(14).

Mr. S. Sciatica. March 31st, 1938.

Time	Serum potassium in mg. per cent.
9.30 a.m. - potass. chloride gr.75	14.6
11 a.m.	17.4
12 noon	21.6
1.15 p.m.	19.3

(15). /

(15).

Mr. S. Sciatica. April 9th, 1938.

Time	Serum potassium in mg. per cent.
9.10 a.m. - pot. chloride gr.75	15.7
10.20 a.m. - quinine gr.10 orally	
10.40	18.8
11.40 a.m.	16.0
12.55 a.m.	13.7

Note :- The fall in the level of the serum potassium occurred earlier and was more rapid when quinine was given after the potassium chloride.

Quinine bihydrochloride gr.10 was given orally to one non-myotonic man after fasting for three hours.

(16).

P.S. Age, 30. Neurasthenia. March 28th, 1938.

Time	Serum potassium in mg. per cent.
10.10 a.m. - quinine gr.10 orally	15.7
10.40 a.m.	17.9
11.15 a.m.	16.8
12.15 p.m.	14.3
1.15 p.m.	16.5

Note:- /

Note:- After the dose of quinine the level of the serum potassium remained above the initial level except for one sample takentwo and a half hours after the dose.

From a study of Tables 14, 15 and 16 one cannot come to any definite conclusions. The impression from one experiment only (Tables 14 and 15) is that quinine accelerates the excretion of ingested potassium. Table 16 confirms the impression already formed from a study of Tables 7, 8, 9, 11 and 13 that the only possible suggestion that can be made is that quinine may draw potassium from the tissues into the serum and accelerate its excretion.

How difficult it is to draw any conclusion is well illustrated by the figures in Table 17 which gives the level of serum potassium in the myotonic patient W.W. over a period of three hours following a twelve hour fast, and Table 18, which shows the serum potassium level on another morning during which hard exercise and a meal of bread and milk were taken.

(17). /

(17).

W.W. Myotonia. Fasting 12 hours. May 5th, 1938.

Time	Serum potassium in mg. per cent.
9.15 a.m.	17.14
10 a.m.	19.67
11 a.m.	22.48
12 noon.	16.29

Note:- During this time there was no change in the degree of myotonia.

(18).

W.W. Myotonia. Fasting 3 hours before first sample. May 9th, 1938.

Time	Serum potassium in mg. per cent.
10.5 a.m.	19.1
Hard exercise for 30 minutes	
10.35 a.m.	16.8
11 a.m.- Meal of bread and milk	
12 noon	12.92

Note:- No change in degree of myotonia in muscles of eyelids during the period of observation, but immediately after the exercise there was no voluntary myotonus in the leg muscles.

Considering as a whole all these experiments in connection with quinine and the serum potassium, (Tables 7 to 18) the one definite statement which can be made is, as mentioned before, that the level of the serum potassium has no relation to the degree of myotonia. This accords with the view expressed by Harvey (1938) who said that in Baltimore, U.S.A., using Kramer and Tisdall's method for estimation of serum potassium, they were unable to show any consistency in the changes in the level of the serum potassium in the blood of myotonics after quinine.

Although the action of quinine in myotonia is apparently not by means of any effect it may, or may not, have upon the level of the serum potassium, I think it probable that quinine does indirectly affect the level of the serum potassium. Hughes (1925) found that quinine in anti-malarial doses in man (0.6 to 1.0g.) produces a fall in the blood sugar. Given intravenously the hypoglycaemia occurs almost at once, but after oral administration there may be no change in the blood sugar for a half to one hour. Hughes found that quinine produces a rise in the blood sugar in rabbits. In discussing his findings he /

he said that the evidence seems to show that quinine influences the level of the circulating glucose in two ways, one by stimulating the sympathetic system and so, probably, causing a secretion of adrenalin leading to hyperglycaemia, and the other by causing a liberation of insulin with resultant hypoglycaemia. With large doses in rabbits both effects are produced but the former predominates and the net result is a rise in the blood sugar. With smaller doses either there is no sympathetic stimulation at all, or it is so little that in many cases the net result is a hypoglycaemia.

We have already seen that the metabolism of glucose causes changes in the level of the serum potassium, which falls as sugar is withdrawn from the blood. If quinine causes changes in the blood sugar level it must also affect the level of the serum potassium, and it would seem that its effect on the serum potassium would vary according to the dose.

THE EFFECT OF BEER, INSULIN AND CORTIN ON MYOTONIA. WITH FIGURES FOR SERUM POTASSIUM.

The clinical effect of beer, insulin and an adrenal cortical extract named Cortin (Organon Laboratories) /

Laboratories) was investigated on the patient W.W. The observation that beer improves myotonia (Russell, 1936) has been confirmed by Foster Kennedy and Wolf (1938). Insulin and Adrenal cortical extract were tried because, if potassium affects myotonia, it was thought that, as insulin and adrenal cortical extract (the latter in Addison's disease if not in the normal) both lower the serum potassium, they might have some effect on myotonia.

Samples of blood for serum potassium estimation were taken before and after the beer and the Cortin: no samples were taken when insulin was given as it is known to depress the serum potassium.

(19).

W.W. Myotonia. Fasting 4 hours. March 14th, 1938.

Time	Serum potassium in mg. per cent.
12 noon - Then drank one pint of ale	14.49
1 p.m.	14.49

Note:- No change in myotonia.

(20). /

(20).

W.W. Myotonia. Fasting 4 hours. March 15th, 1938.

Time	Serum potassium in mg. per cent.
12 noon - Then drank two pints of ale	16.0
1 p.m.	13.76

Note:- No change in myotonia.

(21).

W.W. Myotonia. Fasting 12 hours. May 7th, 1938.

Time	Serum potassium in mg. per cent.
9.30 a.m.	16.01
9.45 a.m. Cortin 10 c.c. intramuscularly	
10.30 a.m.	15.17
11.30 a.m.	12.08

Note:- No improvement, or change in degree of myotonia.

No clinical change of any kind was found after giving beer (in amounts up to two pints), insulin or Cortin. Russell (1936) found the improvement after beer when it was given to a man with myotonia congenita. /

congenita. As I shall show later, it is probable that W.W. is suffering from dystrophia myotonica. Possibly beer only affects the myotonia of myotonia congenita. Kolb, Harvey and Whitehill (1938) gave adrenal cortical extract (Wilson), 18 c.cm. to a patient with dystrophia myotonica and found no discernible change.

It will be seen (Tables 19 and 20) that, although there was no change after one pint, the serum potassium level was considerably lower after taking two pints: it was also lower after the injection of Cortin. These figures (Tables 19, 20 and 21) add to the weight of the evidence that there is no relation between the level of serum potassium and the degree of myotonia. Myotonia was just as pronounced when the serum potassium was 12.08 mg. per cent (Table 21) as it was when the level was 25 mg. per cent (Table 13).

THE EFFECT OF BEER AND QUININE ON TWO OTHER MYOTONIC PATIENTS.

Through the courtesy of the surgeon in charge I was able to examine two myotonic patients who were were /

were admitted to hospital for surgical treatment following injuries. One of them, H.C., who had myotonia congenita, was a most willing subject but he was only in hospital over a weekend. The other, D.F., who had dystrophia myotonica, was in hospital much longer but, after two samples of blood had been obtained from him, he refused to allow any further examination of any kind. My observations on these two patients are, therefore, limited.

Both these patients improved with quinine bi-hydrochloride gr.10 by the mouth, but the improvement obtained was slower and less pronounced than with a similar dose of quinine taken by W.W.

Beer was not given to D.F., but one pint of Dalkeith ale (of which two pints had no effect on W.W.) caused great improvement, both subjective and objective, in H.C., the effect being greater than that produced by quinine. At the end of one hour there was no myotonia in the eyelids or hands after tight closing. In contrast with this, I was unable to demonstrate any objective improvement in H.C. after quinine, although he always maintained that he felt less stiff.

It /

It is interesting to note the contrast between W.W. and H.C. Quinine had a great effect on W.W. and little effect on H.C., whereas H.C. was much better after one pint of ale, of which two pints had no effect on W.W.

(22).

D.F. Age, 55. Dystrophia Myotonica. Fasting 12 hours. May 23, 1938.

Time	Serum potassium in mg. per cent.
9.40 a.m. Quinine gr.10 orally	19.67
11.40 a.m.	16.57

Note:- Less myotonia in eyelids after two hours. Subjective improvement in rest of body.

(23).

H.C. Age, 23. Myotonia Congenita. Fasting 12 hours. May 21, 1938.

Time	Serum potassium in mg. per cent.
10 a.m.	16.01
10.5 a.m. One pint Dalkeith Ale	
10.20 a.m.	16.29
10.40 a.m.	15.45

Note:- Clinical improvement in thirty minutes. Less myotonus in muscles of hand after tight gripping. No spasm of M. frontalis after tight closing of eyelids. Subjectively much better. Improvement lasted about one hour.

(24). /

(Table 24).

H.C. Age, 23. Myotonia Congenita. Fasting 12 hours. May 30th, 1938.

Time	Serum potassium in mg. per cent.
10 a.m. - quinine gr.10 orally	16.86
10.30 a.m.	16.29
11.30 a.m.	15.17

Note:- No improvement at 10.30 a.m. At 11.30 a.m. (1½ hours) slight improvement; neck less stiff, but still had spasm of frontalis M. on tight closing of eyelids. No further improvement but effect lasted about six hours.

In Table 23 it will be noted that there is clinical improvement after ale without significant change in the serum potassium. In Tables 22 and 24 there is in both cases a slight depression of the serum potassium after quinine was taken. All that can be said about these figures is that they add further to the evidence that there is no correlation between the degree of myotonia and the level of the serum potassium.

It may be added here that, although quinine and alcohol were shown to relieve myotonia, neither of them had any effect on muscular weakness.

THE /

THE ACTION OF QUININE AND ALCOHOL IN MYOTONIA.

These studies in myotonia were undertaken in order to test the effect of various drugs or agents on myotonia, and in the hope that some light might be shed on the mode of action of quinine. According to Adie and Greenfield (1923) the myotonia of myotonia congenita and dystrophia myotonica are identical, so that for purposes of investigation it was immaterial that my three subjects were not all suffering from the same disease.

In the historical summary (page 39) mention has already been made of the work of Weiss and Kennedy (1924), Pamboukis (1930), Lindsley and Curnen (1936), and their attempts to explain the pathology of myotonia; and of Wolf's (1936) discovery of the specific action of quinine, since confirmed by many others.

Among other observations that have been made on myotonia we must mention the following. Kolb, Harvey and Whitehill (1938) gave a patient para-

thormone /

parathormone (parathyroid extract, Lilly) in doses of from 5 to 9 c.cm. daily for one week: during this time the serum calcium rose from 10.2 to 11.4 mg. per cent and the phosphorus decreased from 3.2 to 2.9 mg. per cent without any observed change in the myotonus. I might here mention that the serum calcium content was examined in W.W. and D.F. and in both cases was 10.5 mg. per cent. Although Pamboukis (1930) claimed relief in some cases with calcium it does not seem possible to explain myotonia on the basis of a calcium disturbance.

It has been mentioned (page 39) that Weiss and Kennedy (1924) obtained relief by giving thyroid followed by atropine. Poncher and Wade (1938), however, found thyroid therapy ineffectual in two adults, but it slightly improved a child and after prolonged use led to complete relief in an infant. Poncher and Wade (1938) also confirmed a statement of Pansini that adrenaline made myotonia worse, and they also found that benzedrine made their patients worse. Pilocarpine had no effect on their patients; whereas Lindsley and Curnen (1936) and Pamboukis (1930) found an increase in myotonus and Monrad-Krohn (1930) a decrease in myotonus after pilocarpine.

In /

In view of these conflicting statements the observation of Collier, Adie and Walshe (1937) that "there is no treatment known to benefit this disease specifically" was undoubtedly a just one. Since that statement was made it has been established beyond doubt that quinine is a specific agent, and that alcohol acts in some cases.

Dr. Ritchie Russell and Dr. Edgar Stedman (1936) stated that they were quite unable to explain the action of alcohol in myotonia. It has been suggested (Harvey 1938) that, as beer contains plenty of magnesium, its action might be dependent on the magnesium content. Corkhill (1938) has shown that magnesium produces a hyperglycaemia in rabbits. Magnesium, therefore, may have some influence on carbohydrate metabolism in the human. However, the serum magnesium level was 2.3 mg. per cent in two of my patients in whom it was examined (W.W. and J.C.), and apparently in all myotonics in whom it has been examined it has been within normal limits: furthermore, Dr. Ritchie Russell (1936) found that pure ethyl alcohol reduced myotonia. There is, thus, no support for the magnesium theory.

Carbohydrates /

Carbohydrates and beer are known to precipitate attacks of familial periodic paralysis. The patient H.C. who improves after beer, also improves for about two hours after meals; this superficially suggests the possibility that the improvement is due to some mechanism similar to the action of beer and meals in familial periodic paralysis. But the improvement is not due to weakness and, furthermore, as shown later (page 110) myotonus may persist in paralysed muscles. Again, beer reduced the level of the serum potassium much more in W.W. (Table) in whom it had no clinical effect, than in H.C. (Table) in whom it reduced the myotonia; and meals and glucose did not improve W.W. or H.C. My impression is that the action of alcohol is directly on muscle, and that meals may possibly act in some obscure way in some persons by affecting the potassium ratios.

Various attempts have been made to explain the action of quinine. There is, to begin with, a dispute as to whether the myotonus of myotonia congenita and dystrophia myotonica has a neurogenic or a myogenic basis. Lindsley and Curnen (1936) in their electro-myographic study produced evidence suggesting /

suggesting that the after contraction of myotonia is of reflex origin and is due to the persistent discharge of hyper-excitable sensory end-organs in muscle. Wolf (1936) in his original report, therefore, suggested that quinine acts by diminishing reflex action.

Some think that the disturbance in myotonia is at the myoneural junction, and Foster Kennedy and Wolf (1937) suggested that quinine inhibits acetylcholine at the myoneural junction. This explanation has not been experimentally proved, but there are several observations which are suggestive. Quinine exaggerates myasthenia and prostigmin aggravates myotonia (Russell, 1936), (Harvey and Whitehill, 1937), (Foster Kennedy and Wolf, 1938). It has been shown that when these two drugs are given simultaneously in myotonia their action is mutually antagonistic (Kolb, Harvey and Whitehill, 1938). Now it is thought (Blake Pritchard, 1935) that the action of prostigmin is at the myoneural junction where it delays the destruction of acetylcholine by the choline esterase of the blood. Furthermore, Starr (1936) has shown that quinidine, the isomer of quinine regularly/

regularly diminishes or abolishes the ability of acetylcholine to slow the heart rate. These observations are in favour of the suggestion that the action of quinine is at the neuro-muscular junction.

The myotonic reaction has long been compared with the delayed relaxation of muscles which have been poisoned by veratrine. According to Sollmann (1936) veratrine produces a powerful constriction of the peripheral blood vessels which may be removed by atropine or quinine. It has also been known for many years that quinine has a direct effect on skeletal muscle, increasing its refractory period and causing fatigue and depression of contractibility and irritability. Again, according to Sollmann, "quinine tends to concentrate at the surface of solutions:" these rather rigid films interfere with the condensation of other substances at the surface, and, therefore, hinder catalytic phenomena, inorganic as well as organic. Thus there is a decrease in metabolism. The quinine film presumably diminishes the permeability of the cell and thereby leads to a narcotic action such as is seen on local application to nerves and muscles. It is, therefore, possible that /

that the action of quinine in myotonia may be directly on the muscle, either by a local vaso-motor mechanism or by a physico-chemical action at the cell membrane.

There is yet another way in which quinine might act in myotonia. Dr. Mary Walker (1938) made the following demonstration in a patient with myasthenia gravis. After the effect of prostigmin had been allowed to wear off, the circulation in both arms was shut off by inflating the sphygmomanometer cuffs to 200 m.m. mercury. Pronation and supination of the forearms was carried out until the patient became tired (in about a minute). Release of pressure in the cuffs led, after an interval of about ninety seconds, to drooping of the eyelid, and in about two minutes to weakness of the muscles generally. This has led to the hypothesis that the action of prostigmin in myasthenia gravis may be due to antagonisation of a curare-like substance circulating in the blood and so interfering with transmission of impulse by acetyl-choline, instead of the hypothesis that prostigmin acts by inhibition of choline esterase at the myo-neural junction. Analogically, therefore, one might postulate that myotonia is due to some substance circulating /

circulating in the blood and that quinine antagonises or destroys it in the blood.

Foster Kennedy and Wolf (1937) gave spinal anaesthesia to a patient with myotonia congenita as he lay on his right side; the right leg was very soon paralysed and insensitive to pinprick, while the left leg was normal. At this stage the myotonic reaction to mechanical and electrical stimulation of the gastrocnemius muscles was equally marked on both sides, and remained so as both sides became paralysed and analgesic. Quinine bihydrochloride gr.10 was then given intravenously and the myotonic reaction almost completely disappeared from both legs. This experiment showing that myotonus can remain in a parlysed limb suggests that the disturbance is due to physico-chemical cellular changes in the muscle itself.

I must here mention a suggestion made by Harvey (1938). He postulates that, in the normal person, there is curare-like substance liberated on muscular action which prevents myotonus. Myotonia is always less marked after exercise. The theory is that myotonics are short of this curari-like substance, which /

which is only produced in sufficient quantity to last just a short time after exercise. That the disturbance is local is further suggested by Harvey's observations in Baltimore, U.S.A., on a myotonic who obtained relief in one arm some hours before relief in the other arm after a single dose of quinine. The neurologists in Baltimore have discovered a number of goats which were thought by a psychologist to be subject to epileptic fits on being frightened; on attempting to jumb fences they fell down. It has been proved that they are suffering from true myotonia, and they are, at present, being bred for research purposes. It is to be hoped that investigations possible on goats, but not on human beings, will very soon lead to great advances in our knowledge of myotonia.

In the meantime I think that the trouble in myotonia is an inborn error of metabolism causing secondary intracellular muscle defects, and that the balance of evidence is in favour of the theory that the action of quinine is a physico-chemical one on the cell membrane.

MIGRAINE AND FAMILIAL PERIODIC PARALYSIS.

In the course of my reading of the literature of familial periodic paralysis I have been struck by its relation to migraine; and because migraine is such a common and disabling disorder, the cause of which is still unknown, an analysis of this association seems to be worth recording.

Holtzapple (1905), in describing the largest personal series of cases of familial periodic paralysis yet reported, was particularly impressed by the association with migraine. His patients were all members of one family among whom many had periodic sick headache which"appears to be equivalent to an attack of paralysis, both having a common cause whatever that might be." During Holtzapple's observations over twenty-two years on four generations of this family he found thirty-two persons with either headache or paralysis, of whom fourteen had paralysis only and thirteen had headache only, and five suffered from attacks of both headache and periodic paralysis.

Collier, Adie and Walshe (1937) have stated that only in this family reported by Holtzapple was migraine associated: but I find that this association has /

has been noted by many other observers.

Gardner (1912) observed for five years a young collier whose attacks of periodic paralysis began at seventeen and "seem to have replaced previous attacks of bilious headache." In discussing familial periodic paralysis Gardner went on to say:-

"Amongst the many well known hereditary diseases those which most resemble it are epilepsy, migraine and gout. There are other periodic disorders which show no tendency to be hereditary and which do not appear as family diseases. The most striking of these is ophthalmoplegic migraine which, in some respects, is closely analogous to periodic paralysis and is also a rare disease. These cases are much more closely analogous to periodic paralysis, especially in regard to the following points:-

1. The attacks are periodic in their occurrence and tend to appear at more and more diminished intervals.
2. They are almost invariably associated with headache, often exactly like ordinary migraine.
3. They are accompanied by a form of paralysis which is quite temporary in its nature, and at first disappears completely between the attacks.
4. As a consequence of repeated attacks some paresis may persist during the interval and eventually partial, /

partial, or even total permanent paralysis may supervene. This is exactly what happened in some of Holtzapple's cases of periodic paralysis who lived on into old age, though the onset of permanent paralysis was much slower in these cases than in ophthalmoplegic migraine.

5. Cases of periodic ophthalmoplegia have been reported in which the paralysis alone occurred without headache or vomiting.

6. Ophthalmoplegic migraine, like periodic paralysis, is, to a certain extent, amenable to treatment. A case in the writer's care was quite free from attacks while under treatment in hospital for some months for an intercurrent affect; and the paresis of the muscles affected, which had persisted between the attacks, almost entirely cleared up. After he had returned to his old home conditions, however, the attacks recurred, and soon became as bad as ever."

Zabriskie and Frantz (1932) described an individual with typical attacks of familial periodic paralysis whose mother and maternal grandmother both suffered from migraine.

MacLachlan (1932) described a family of whom six had /

had periodic paralysis and two of these suffered from migraine. He stressed very strongly the association with migraine.

Schoenthal (1934) described a family of whom some had attacks of periodic paralysis and two suffered from severe attacks of headache.

Biemond and Daniels (1934) described a Dutch family of whom fourteen had periodic paralysis, and four had periodic headaches resembling migraine.

It may be said, in explanation of the instances I have quoted of the association of migraine and familial periodic paralysis, that they are due to the expected incidence of a common malady upon a rare condition; but migraine appears to be commoner in periodic paralysis than in the general population.

Apart altogether, however, from their incidental association, there is much similarity in the causes and clinical features of both.

Heredity is marked in familial periodic paralysis and has been traced through five generations; several members of the family are usually affected, although sporadic cases have been described. Heredity is a very important factor in migraine (Bramwell, 1926); and migraine often affects several /

several members of the same family, sometimes showing the same clinical features in one family.

The commonest age of onset of both diseases is about puberty, and both are periodic in their attacks. The severity and frequency of migraine becomes less in middle age, and it usually disappears in old age. Holtzapple (1905) found that attacks of periodic paralysis become less frequent and more irregular after middle age; and Collier, Adie and Walshe (1937) stated that there is an invariable tendency for the attacks to diminish in frequency and severity after middle life.

Most attacks of familial periodic paralysis begin in the early morning, and they may last from one hour to one week (Taylor, 1898). Similarly, most migrainous subjects either wake up with severe headache, or wake up knowing they will shortly have a headache, which may last for a few hours or several days.

The association of a heavy meal and hard exercise with attacks of familial periodic paralysis is well recognised. One of Holtzapple's patient often had a voracious appetite which, if satiated by rich /

rich food, precipitated an attack during the night. The attacks of the patient described by Gardner (1921) nearly always occurred after hard exercise and a heavy meal with beer, sausages and cheese. Exertion was mentioned by Taylor (1898). The association of food has been noted by Zabriskie and Frantz (1932), Biemond and Daniels (1934) and others. Cold and emotions as precipitating factors have been noted by Zabriskie and Frantz (1932), MacLachlan (1932), Biemond and Daniels (1934) and Schoenthal (1934).

Less is known about the cause of attacks of migraine. Minor refractive errors must occur in many people without causing migraine. Mental stress and strain is probably a factor, as attacks are usually less frequent on holiday, but if three-quarters of all cases of migraine start before the age of twenty (Bramwell, 1926) it is difficult to blame the stress and strain of life. Collier, Adie and Walshe (1937) suggest that it is the result of a temporary condition of intoxication from a digestive, metabolic or internal secretory disorder which recurs periodically. Balyeat (1933) mentions theories under these headings:- reflex, central duodenal stasis, /

stasis, hypophyseal, toxic, endocrine gland, vaso-motor and allergic.

But, in my opinion, the influence of a deficient digestive function, possibly on some underlying metabolic defect, is very important and Balyeat said that it is believed by many that carbohydrates have much to do with precipitating an attack. MacLachlan (1932) has said, in discussing the association of familial periodic paralysis with migraine: "As in migraine, patients often say that on the day preceding an attack they have felt exceptionally well, and have not only accomplished an active day's work, but have taken exercise in addition. Similarly, bulimia is frequently present and relatives have found noteworthy the amount of food required to satisfy the patients' appetite on these days." I myself have been impressed by the number of migrainous subjects whose attacks are especially liable to appear in the morning after hard exercise, followed by a good meal, in cold weather on the previous day.

Collier, Adie and Walshe (1937) in defining migraine state: "less common symptoms of the disease are peculiar slow sensory aurae, which occur in no other malady." But Holtzapple (1905) described in his /

his patients with familial periodic paralysis such prodromal symptoms as a peculiar heaviness, a tired feeling in the extremities, numbness and fomication: "some feel impelled to stretch themselves." And Taylor (1898) mentioned prodroma such as "weariness, sweating, numbness, fomication, headache, backache, somnolence, rapid pulse with a normal surface temperature of the head, body and arms, and an icy cold temperature of the legs, associated with great pallor suggesting a vaso-motor disturbance of a violent sort:" he also quotes Goldflam as mentioning a feeling of coldness in the legs. There was a prodromal "creepy feeling" or numbness in Zabriskie's and Frantz's (1932) case. Schoenthal (1934) found in his adult cases prodromal symptoms such as aurae of paraesthesiae, fatigue, perspiration and a feeling of fear. Most of these prodroma are also found in migraine; and, in addition, soreness of muscles is well recognised in both.

It is well known that temporary paralyses may occur in migraine in the form of a monoplegia, hemiplegia or an ophthalmoplegia, Gardner's description of which I have already quoted. Zabriskie and Frantz (1932) produced a monoplegia in their patient /

patient with familial periodic paralysis by the simple expedient of immersing the arm in water at 14°C. for thirty-five minutes, so that, although all four extremities are generally involved in the attacks of periodic paralysis, the paralysis may occur in one or more limbs as in migraine.

The foregoing consideration of the association of migraine and familial periodic paralysis convinces me of the truth of Holtzapple's remark that both have "a common cause whatever that may be." Now that we know that attacks of familial periodic paralysis are associated with a depression of the serum potassium, there is surely enough evidence to warrant an investigation of the serum potassium in migrainous subjects before and during their attacks. But there are difficulties, as MacLachlan (1932) has said in discussing the investigation of attacks of periodic paralysis: "as in migraine which has some points in common with familial periodic paralysis one encounters insuperable difficulties in investigating the attacks, as these do not occur during the period of physical and mental rest with regular simple meals associated with residence in hospital." It is of interest here to note that ergotoxin abolishes the effect of adrenalin /

adrenalin in raising the level of the serum potassium in cats (Da Silva, 1934). It has also been shown by Marenzi and Gerschman (1937) that ergotamine prevents the adrenalin rise; and by Houssay, Marenzi and Gerschman (1937) that the effect of splanchnic excitation in raising the serum potassium level of dogs is prevented by preliminary ergotamisation. In man, Castleden (1938) has shown that adrenalin causes a fall in the level of the serum potassium. It may well be that in migraine there is a fall in serum potassium due to hyper-secretion of adrenalin from emotion or other cause, and that ergotamine tartrate stabilises the level of serum potassium as it appears to do in animals.

This is admittedly rather speculative but these observations, at least, suggest that ergotamine tartrate, which is a specific for migraine, may have an effect on the serum potassium when given to human beings, and may even relieve migraine by some action on the serum potassium assuming for the reasons I have given that migraine and familial periodic paralysis have a common cause, and that in both there is a fall in the level of the serum potassium.

COMMENTARY ON THE THREE MYOTONIC SUBJECTS.

An interesting group is formed by W.W., D.F., and H.C. as it includes typical cases of myotonia congenita and dystrophia myotonica, and a case illustrating the early stage of dystrophia myotonica: there are also some points to note in each person.

H.C. has true myotonia congenita. The myotonia in him and in the three affected brothers was at its worst about puberty, and is now less marked in all, having disappeared completely in one brother. The youngest sister is said to be slightly affected; according to H.C. she is the only female affected member of the family. Four brothers and sisters of his generation have never been affected. In H.C. there are no signs of bodily dyscrasia.

The patient D.F. was originally described by the late Sir Byrom Bramwell (1909) as a case of Thomsen's disease with hysterical symptoms, but the diagnosis was considered difficult because there was only slight myotonia and he was rather hysterical. He then had spasm of the orbiculares oculorum and difficulty in relaxing after gripping. He was under the /

the care of Soma Weiss and Foster Kennedy (1924) when he was greatly handicapped by his condition, myotonia interfering with walking, and the abdominal muscles being tonically contracted for ten to fifteen minutes after coughing. At that time the diagnosis of Thomsen's disease was questioned, but it was still considered the correct diagnosis because of the early age of and the general distribution of the myotonia; in spite of the fact that he had fronto-parietal baldness, was impotent and showed other signs of glandular and autonomic disturbances; he sweated very easily, had a slow pulse and improved after atropine and thyroid. The sternomastoids were poorly developed, but Orzrchowsky was cited as stating that every case of myotonia congenita showed some muscular weakness and atrophy.

D.F. at fifty-five years of age still has very definite myotonia; but the most obvious feature now is the muscular wasting and weakness which troubles him as much as, if not more than, the myotonia.

The late Sir Byrom Bramwell said of him: "highly neurotic, he seems to have read everything that has been published on Thomsen's disease and to have tried almost /

almost every drug that has been recommended in the treatment of nervous diseases." Now he appears to have more than a pure neurosis. His temperament is peculiar and "difficult". For some minutes he will talk cheerfully about his troubles and all the various drugs that have been tried; and then, for no apparent reason, he refuses to discuss the matter any more, and even starts making accusations about improper treatment. He even threatened to write to the newspapers to expose some imaginary scandals.

His intelligence was below average, and there has probably been some intellectual deterioration. This accords with the view expressed by Maas and Paterson (1937) that, in dystrophia myotonica where there is much muscular wasting there are almost always mental changes.

In contrast with patients with myotonia congenita (Thomsen's disease) who very often "grow out of their troubles," as in the case of H.C. and his brothers, D.F. has developed increasing atrophy, the myotonia becoming at the same time less conspicuous.

The early onset of the disease in D.F. was thought to exclude the diagnosis of dystrophia myotonica, /

myotonica, but Keschner and Finesilver (1925) record the case of a girl who had the first manifestations of dystrophia myotonica at six years. Most persons with dystrophia myotonica die, usually from tuberculosis, before they are forty-five, and Collier, Adie and Walshe (1937) state that the oldest patient reported in the records as still living was fifty, and D.F. is fifty-one. But Kolb, Harvey and Whitehill (1938) mention that one man was still living at fifty-nine in the U.S.A.

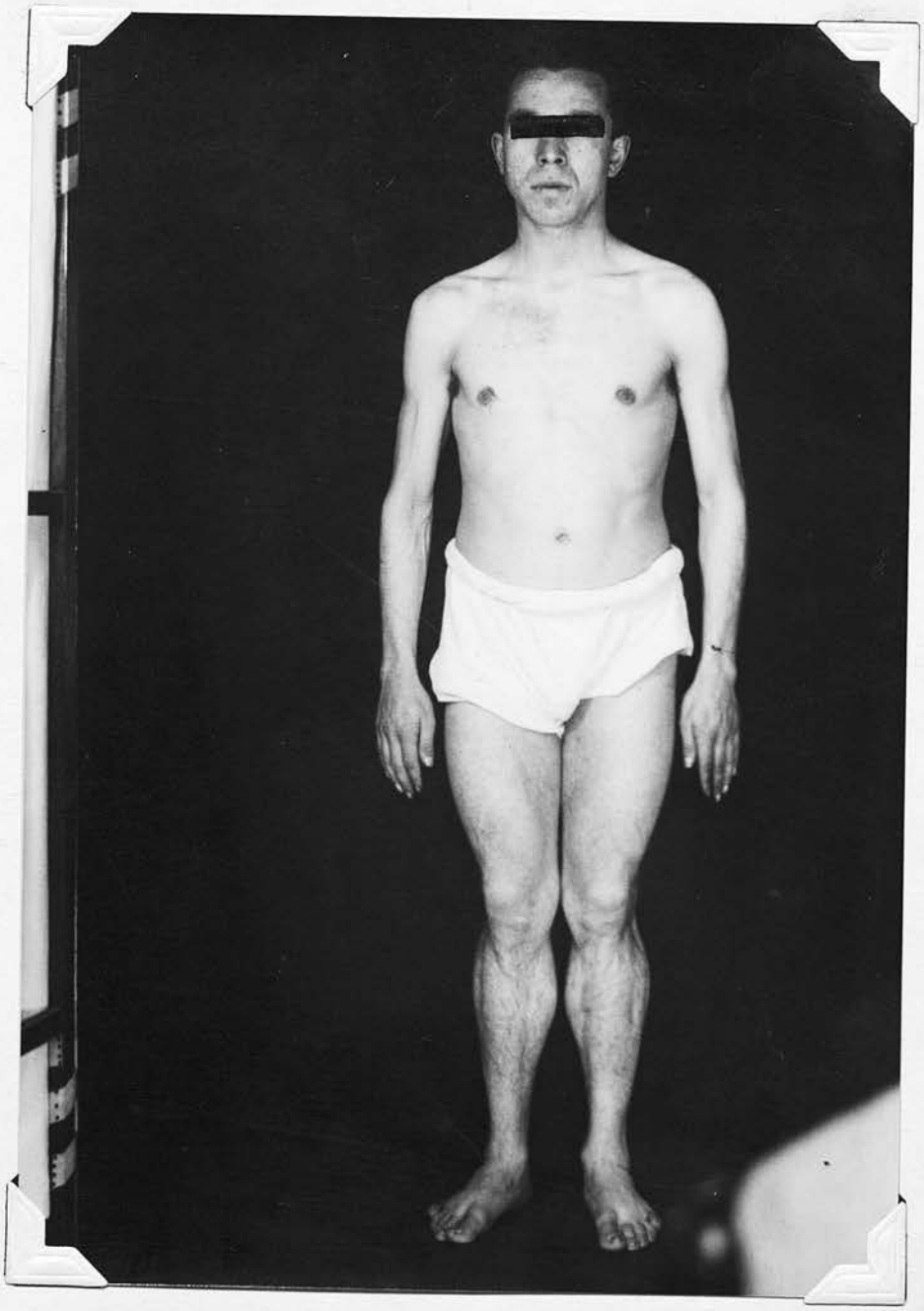
A consideration of the history and clinical features of W.W. makes a diagnosis of pure myotonia congenita impossible. According to W.W. none of his relations have myotonia, premature baldness or early cataract. The very early onset at three years must be very unusual for dystrophia myotonica, but I have already mentioned Keschner and Finesilver's case in which the onset was at six and Maas (1937) mentions five persons with dystrophia myotonica whose symptoms began before ten years.

There is not normally much muscular weakness in myotonia, but every muscle in W.W. was weaker than normal, including the hypertrophied leg muscles. His /

His sternomastoid and pectoralis muscles were very wasted and on electrical examination shown to be atrophied. The contrast between the hypertrophied leg muscles and the wasting of the muscles of the arms and shoulder girdle is well seen in the photograph. He had no ptosis, sunken temporal fossae or wasting of any facial muscles, but Maas (1937) in a series of fifty cases of dystrophia myotonica found two with no wasting of face muscles.

Although his testes were small, he was not impotent. He had no cataract or lens opacity on slit lamp examination, but, according to Curschmann (1912), cataract is found in only thirty per cent of cases of dystrophia myotonica.

Orzrchowsky (1921) has said that muscular weakness and atrophy occur in every case of myotonia congenita, but most others take the view that pure myotonia congenita is very much more rare than dystrophia myotonica; and Maas (1937) maintains that sufficiently careful examination will establish dystrophic signs in most cases of myotonia. I think that W.W. is in an early stage of dystrophia myotonica.



CASE ABSTRACTS.

CASE 1.

W.W. Age, 25.

COMPLAINT. Stiffness of the muscles, mainly of the legs for as long as he can remember.

HISTORY. His early development was normal and he was not late in learning to walk. But very soon after he first began to walk, when he was about three years old, his parents noticed that his legs seemed stiff when he was walking, and that he appeared to drag his left leg. They at first attributed this to a rupture, for which he was operated upon about this time. It soon became apparent, however, that all his movements were slow, stiff and rather clumsy. As he grew older he himself noticed that he fell very easily, and he was so easily knocked over by anyone bumping into him that he could not take part in any games at school. When he was in class at school and was told to stand up, he could not do it quickly; but after he had stood up once, slowly and with some difficulty, he could sit down and stand up again fairly quickly. While at school he was regarded as a very strong boy.

After leaving school at the age of fourteen he says his shoulder and arm muscles did not seem to develop any further, but that his leg muscles developed /

developed very well. At the same time he thinks his arms became weaker, quite apart from any stiffness in them. He has never noticed any increased weakness in his legs, which have always been much more stiff than his arms.

His own description of his condition is that his muscles do not relax properly, but on repeating a movement relax much more quickly. He is very stiff when he wakes up in the morning, and cannot jump out of bed like a normal person. But after about fifteen to twenty minutes he is quite supple. He is always more stiff after sitting down or lying down for more than a few moments. At the end of an ordinary day's work he will be stiff after he has rested for about twenty to thirty minutes. But if he has had an unusual amount of exercise, such as a sharp six mile walk, he becomes stiff in about ten minutes after stopping the exercise and resting.

On attempting to go upstairs he becomes very stiff at about the third or fourth step: if he perseveres, the stiffness passes off in two or three more steps and his pace upstairs increases. That this stiffness on going up steps always come on at the same point is neatly demonstrated by his experience on /

on boarding two different types of bus. He can easily board one with three steps of 3" each, but he has the greatest difficulty in boarding another type of bus which has three steps of 7" each. The amount of exercise on the level previous to his attempts at going upstairs makes no difference to the level at which the stiffness comes on. He never has any difficulty in going downstairs.

He can run fairly well if he first of all takes a very brisk walk, but he can never run as quickly or as steadily as a normal person.

When he is warm he is not so stiff as when he is cold. He says he is always more stiff in wet weather. While he was in the Ward other patients noticed his increased stiffness on rainy days.

As mentioned above he is very stiff on awakening in the morning, but, apart from the effects of rest, he notices no difference in stiffness according to the time of day. The taking of food makes no difference to the stiffness, from which he is never entirely free, there being always a certain amount of residual stiffness. He says he has noticed no change in the stiffness for as long as he can remember, but that his /

his arms and back seem to have become weak in the last few years. His defects do not trouble him so much now as when he was a child: he has learned to look after himself, and does not get over-balanced nearly so frequently.

Apart from the fact that he sweats very easily he has no other symptom of any kind.

PREVIOUS HISTORY. Right inguinal herniotomy at 3-4 years.

Tonsillectomy.

Measles and whooping cough.

FAMILY HISTORY. Father and mother alive and well.

Two brothers a. and w., aged 28 and 20; the elder is married and has two children.

One sister - aged 18 - single.

One of his father's brothers had very large calf muscles and was a wrestler and an artist's model in his younger days. He is now about 45 and is quite normal.

Patient's father had six brothers and one sister: his mother had three sisters.

There is no family history to be elicited of any relation suffering from myotonia. None of them had premature baldness, nor, as far as he knows, any sign of cataract.

Habits /

Habits - Cigarette smoker (ten a day).
Practically teetotal.

EXAMINATION. Healthy looking well nourished man of average build. Hair on head is thick but there is definite frontal baldness. Apart from the axillary and pubic regions, in which the hair is scanty, his body is almost hairless. Average intelligence. Height - 5 ft. 7". Weight 10 st. 6 lbs. Thinks he has lost weight.

There is no wasting of the facial muscles, and there is no hollowing of the cheeks. No obvious wasting of muscles of the neck.

The muscles of the shoulder girdle, arms and chest look poorly developed in contrast with the thigh and calf muscles. In particular the sterno-mastoids, pectorales major and minor are wasted. Biceps and triceps and interossei of both upper limbs are very poorly developed. Supra-spinati and infra-spinati are also wasted.

In marked contrast with this symmetrical generalised wasting of the upper part of his body, apart from his face, the muscles of both legs are symmetrically hypertrophied. In particular, both quadriceps, extensors and both solei and gastrocnemii are /

are very prominently developed.

No involuntary muscular movements. No fibrillation.

Measurements of circumferences of arms and legs in centimetres:-

Rt.	arm	27	Lt.	arm	26.5
	forearm	24		forearm	23.5
	thigh	55		thigh	53.5
	calf	39.5		calf	39
	ankle	21.5		ankle	21.5

Movements are free at all joints. There is no stiffness on passive movement of any joints in the neck, shoulder girdle or arms. There is definite resistance to rapid passive flexion and extension at both hips, knees and ankles.

Increased muscular tone can be easily demonstrated in both thighs and calves. On light direct percussion of the quadriceps extensors or gastrocnemii muscular contraction occurs and lasts up to seven or eight seconds. This myotonic reaction was also obtained on one or two occasions in both brachioradial muscles, but was not so easily demonstrable as in the legs. The myotonic reaction was most easily demonstrated in both eyelids. On active closure relaxation did not occur for nearly ten seconds.

There /

There appeared to be some muscular weakness in all muscles. The weakness was very marked in the upper half of his body, particularly in the sterno-mastoids and pectorales, and less noticeably so but still very marked, in the deltoids, biceps, triceps and small muscles of the hand. Flexion and extension of the spine were very weak.

On testing the biceps or triceps one noticed that the power was fair to begin with, but that it very rapidly deteriorated (in two to three seconds).

If the patient gripped one's hand there was very slow relaxation on his part. Grip with both hands was definitely weak - the dynamometer reading for both right and left hand being less than half that of the average control.

In spite of the muscular hypertrophy in the legs there was very definite weakness of all movements, and more particularly of flexion and extension at the hip and knee joints. There was no inco-ordination of movement. The increased muscular tones prevented rapid repeated movements.

Gait - as detailed in history.

Reflexes.-/

Reflexes:-		R.	L.
	S.J.	Weak	Weak
	B.J.	"	"
	T.J.	"	"
Abd.	Upper.	"	"
	Lower.	"	"
	K.J.	Normal	Normal
	A.J.	"	"
	Plantar.	Flexor	Flexor

No disturbance of organic reflexes.

Nothing abnormal detected in sensory system.

There was definite slight atrophy of both testes. Is not impotent.

Palatal arch was rather high.

Tongue - no wasting.

Teeth. Some caries and pyorrhoea.

Lens of eye - No opacities on slit lamp examination.

Electrical.

17.3.38. Electrical Reactions of muscles.

Calvanism: Myotonic reactions seen in all muscles of both legs; most marked in quadriceps extensors and large muscles of calf. The peroneal muscles reacted more strongly than the anterior tibial muscles.

Response /

Response of left quadriceps extensors to single stimulus:

1st.	Reaction	-	20 secs.
2nd	"	-	15 "
3rd	"	-	12 "
4th	"	-	9 "
5th	"	-	4 "

Note:- Gradual shortening of length of myotonic reaction.

In the arms the deltoids gave the most brisk response. Myotonic reaction was also well marked in small muscles of both hands - interossei, lumbricals, abductor pollicis, abductor minimi digiti.

Myotonic reaction was demonstrated in serrati, trapezius, latissimus dorsi, rhomboids, and muscles of spine-quadratus lumborum.

Galvanic response very slight (no myotonus) with pectorales major and minor, and with both sterno-mastoids.

Faradism: Pectorales Mm. Kcc > Acc. No reaction of degeneration obtained: only a flickering response demonstrated with difficulty.

Quinine hydrochloride, gr. 10 was given at 10.50 a.m. Further tests at 12 noon showed marked diminution in myotonic reaction in thigh and calf muscles. Almost complete relaxation after shutting eyes tightly.

Summary: /

Summary: Atrophy of Pectorales Major and Minor and of sternomastoids. Myotonic reaction in greater or lesser degree in other muscles.

CASE 2.

D.F. Age, 55.

COMPLAINT. Admitted to Hospital on account of fracture of right humerus. Has had weakness and stiffness of muscles since he was twelve.

HISTORY (as related to me) As far as he can remember he was quite well until he was about ten years old when, after an illness lasting about three months and said to be pneumonia, he first noticed stiffness in the legs while lifting a wheelbarrow. Shortly afterwards he found he had to make three attempts to climb a wall before he overcame muscular stiffness. At the same time he developed headaches and constipation from both of which he had been a life long sufferer.

At school he was known as a strong boy and was not greatly troubled by his condition, but it has since been a severe handicap. When he was nineteen he went to the U.S.A.: for the next ten years myotonia was very severe; even a gust of wind would bowl him over. Since he was thirty the myotonia has become less severe.

During /

During his life he has tried many drugs and diets in attempts to improve his condition. He has taken thyroid up to gr. 15 a day with "mental improvement" but no effect on myotonus or on the pulse rate which has always been slow. In the year 1914 he gave himself subcutaneous injections of adrenalin ♏ 7½ a day for two months without effect. He has also had parathyroid gland, mixed pituitary gland and pilocarpine injections without effect.

He claims that he once improved on a high chloride diet with calcium, Viosterol, liver, milk, peas and other green vegetables in abundance. Beer has no effect on him, but he says he once took a gill of whisky which made him worse and caused profuse perspiration. He also says that quinine sulphate gr. 2 to 5 gives him tinnitus without any effect on the myotonia.

Muscle spasm can be overcome by effort in about a minute. His greatest difficulty is in starting to walk or in grasping objects. After coughing his abdominal muscles contract tonically for about ten to fifteen minutes.

The supra-orbital headaches, occurring at intervals /

intervals of six or eight weeks and lasting two or three days, are always left-sided and accompanied by drooping of the left eyelid with lacrimation and watery nasal discharge: during these attacks there is less myotonia. The headaches also are now less severe and less frequent. Spastic constipation is worse when he has a headache.

He also has what he calls "dizzy spells" coming at irregular intervals and lasting nearly a minute, when he practically loses consciousness and following which he has palpitation for a few minutes.

He has been impotent for sixteen years. He sweats easily. He has worn glasses for reading for thirty years.

Food does not relieve his myotonia.

PREVIOUS HISTORY. Measles, scarlet fever, whooping cough, pneumonia.

Appendicectomy when thirty years old.

Previous fracture of right humerus seven years ago. His arm has been broken each time owing to overbalancing as a result of myotonia.

Has been in many hospitals for investigation of his condition.

FAMILY /

FAMILY HISTORY. Father died age 92 - Senility.

Mother died age 67 - "change of life."

Two brothers, both alive and well: one of them is married and has seven children, all of whom are well.

One sister: died aged 65 (unmarried) from arteriosclerosis. She had slight myotonia.

Habits: Cigarette and pipe smoker. Occasional beer.

EXAMINATION. (This was difficult on account of the plaster sling for treatment of the fractured arm).

Intelligence below average. Extremely introspective. Peculiar temperament, almost paranoid. Is unreliable. Pulse rate 58.

Very bald. Skin smooth with very little hair. Hollow cheeks and sunken temporal fossae: "myopathic face." Slight ptosis of both upper eyelids. Thin and wasted looking.

Sternomastoid muscles very wasted. Slight wasting of other muscles of neck, and of the muscles of the face and of mastication. General wasting of muscles of shoulder girdle, left arm and legs, particularly marked in small muscles of the hand and vasti of the thighs and dorsiflexors of the feet. Tongue slightly wasted.

No /

No involuntary muscular movements. No fibrillation.

Movements free at all joints (excluding right arm). No increased muscular tone noticeable on passive movement.

Voluntary myotonia marked in orbiculares oculorum , definite in muscles of mastication, flexors of fingers, opponens of thumb, extensors and flexors of forearm and wrist, extensors and flexors of legs and feet, and in abdominal muscles. Also severe myotonus of pharyngeal constrictors on swallowing. Soft palate unaffected. Occipito-frontalis unaffected.

Percussion myotonus obtained in tongue and in limb muscles.

Reflexes:-		R.	L.
	J.J.	absent	
	S.J.	-	Doubtful positive
	B.J.	-	" "
	T.J.	-	" "
Abd.	Upper.	Absent	Absent
	Lower.	"	"
	K.J.	"	"
	A.J.	"	"
	Plantars.	Flexor	Flexor

No /

No disturbance of organic reflexes. Nothing abnormal in sensory system.

A curious feature in his case is that he cannot maintain flexion at the left elbow against resistance for more than two seconds, but if this is repeated several times, he can maintain flexion for much longer. This same condition was found on dorsi-flexion at the ankle.

He had great weakness of all muscles, especially the peripheral limb muscles.

Atrophy of testes. High palatal arch.

No cataract visible on ordinary ophthalmoscopic examination. Slit-lamp examination not obtained.

CASE 3.

H.C. Age, 23.

COMPLAINT. Admitted to hospital for spinal injury. Has had myotonia for seven years.

HISTORY. He was sixteen when he first noticed the stiffness in the muscles of his arms and legs, and in other muscles. Those members of his family who develop myotonia all seem to get it about or shortly after puberty, and later they improve. He is better than he was and he hopes to be normal before long.

The myotonia affects in varying degree practically all his voluntary muscles. After tight closing of his eyelids he has no difficulty in re-opening them, but he is left for a few seconds with a spasm of the frontalis muscle. He is considerably handicapped by myotonia of his external ocular muscles. If he looks sideways he cannot bring his eyes back to the normal position for about four seconds: if he repeats this movements several times there is then no delay. He also has difficulty in chewing and in swallowing. On going upstairs he becomes very stiff at the first step, and this stiffness does not wear off for nine or ten steps.

A /

A standing start on stairs is very difficult. If he grips anything very tightly for about six seconds he can then release his grip at once. Owing to being unable to release his grip immediately he was once dragged by a bus.

His myotonia becomes much better during meals: this improvement lasts for about two hours. Sweets do not relieve it. Beer relieves the myotonia for several hours. He is less stiff for about an hour after getting out of bed in the mornings. A heavy day's work makes him very stiff at night, but if he misses a day's work he is more than usually stiff in the morning.

PREVIOUS HISTORY. Childhood infections.

FAMILY HISTORY. Three brothers and three nephews have the same condition. One brother and three sisters are unaffected. The youngest sister is said to have slight myotonia. As far as is known neither of his parents have been affected.

EXAMINATION. A well developed man below average stature. No baldness. Average intelligence. No cataract on ophthalmoscopic examination. No wasting of muscles. Obvious hypertrophy of muscles of /

forearms, thighs and calves. Myotonia as detailed in history.

No testicular wasting.

Normal palatal arch.

Nothing abnormal in sensory or other systems.

SUMMARY AND CONCLUSIONS.

In two different branches of neurology there have been in recent years considerable advances in treatment.

In the first group an outline has been given of the extension of our knowledge of the relation of disorders of nutrition to diseases of the nervous system, suggesting that further investigation along these lines may solve some of the problems of incurable diseases of the nervous system.

In the second group, composed of familial periodic paralysis, myasthenia gravis and the myotonias, advances in our knowledge of treatment point the way to further investigations of neurological problems along quite another line. Reasons have been advanced for considering these three diseases to have many features in common. Each of them has been known for about sixty years, and has remained during this time practically unamenable to treatment: but within the last two or three years a specific treatment has been found for all of them. The elucidation of the mode of action of these specific remedies and their relation to neuro-muscular conduction and muscular action emphasises the importance of a physiological rather than a morphological approach to problems in neurology.

Familial /

Familial periodic paralysis, myasthenia gravis and the myotonias have been considered in relation to the potassium ion.

The effect of insulin and glucose on the serum potassium has been investigated, and the findings have been discussed.

On the analogy of deaths from cardiac failure in attacks of familial periodic paralysis, a hypothesis that a very low serum potassium may cause death in diabetic coma has been presented.

Some observations on the effect of quinine, beer, potassium, insulin and adrenal cortical extract on myotonia and on the level of the serum potassium in myotonia have been recorded and discussed, with particular reference to the mode of action of quinine and alcohol in reducing myotonia.

The relationship of migraine to familial periodic paralysis has been traced and the suggestion made that an investigation of migraine in the light of our knowledge of familial periodic paralysis is desirable.

A short commentary has been presented on the points of interest in the three myotonic subjects who were the subject of the investigations.

The /

The following conclusions have been reached:-

1. Oral quinine is a specific for myotonia but seems to act better in some people than in others. Quinine does not affect the weakness in dystrophia myotonica.

2. Intravenous quinine is an undesirable and unnecessary method of treatment of myotonia.

3. Beer improves some myotonics, but is without action on others.

4. The administration of potassium makes myotonia worse.

5. There is no direct relation between the level of the serum potassium and the degree of myotonia.

6. Quinine has no direct effect on the level of the serum potassium, and the action of quinine in myotonia cannot be explained by any action on the serum potassium.

7. Insulin and glucose both depress the level of the serum potassium, and the combined effect is greater than the separate effect of either.

8. The first symptoms of dystrophia myotonica may begin at an earlier age, and the patient may live to a greater age than has been hitherto thought possible.

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