The reasons for singling out the motor-cyclist from among other road users have been given. He rides unprotected and runs a particular risk of injury. The importance of head injury in the mortality rate is obvious, and it is clear from the present trend of figures that any reduction in the mortality rate from head injury among motor-cyclists would not only benefit the group but have a very favourable effect on accident mortality as a whole. One further point which should be mentioned is the economic loss to the country of these young men. In this series of motor-cyclists with head injuries, 56% were between 16 and 25 years of age and 95% were between 16 and 45. This may be compared with an incidence of 27.9% in the 16–25 year group and 55.8% in the 16–45 year group among an unselected consecutive series of 1,000 closed head injuries from all causes. The country can ill afford the injury to and loss of life among these vigorous young men, many of whom are skilled or in training. During 1955, for example, 149 motor-cyclists were admitted to the male accident ward of the Radcliffe Infirmary alone with injuries of all kinds. There were nine deaths. All had head injury, which was the cause of death in seven.

The evidence in this paper, together with earlier work on this subject, seems to leave little doubt that an efficient crash helmet will prevent many minor concussions and lessen the effect of severer injuries. The risks of severe and complicated skull fractures are considerably reduced. It is surely significant that among the number of civilian motor-cyclists admitted in the last two years there have been only two deaths from head injury where an efficient helmet has been worn, and in both cases there were multiple injuries and evidence of severe impact.

There are several lines for further study. The Road Research Laboratory is continuing its work on the design and construction of helmets, and the possibilities of many of the newer synthetic materials available for both the shell and the inner padding need testing. The standards of an efficient helmet for motor-cyclists also require review with their particular problems in mind. Starks (1952) made a useful survey of motor-cycle accidents based on statistics for the immediate preceding years, and a further field survey on the resultant injury to motor-cyclists when the head is struck would be particularly valuable at this period to estimate how useful a helmet is in preventing concussion altogether. In other cases, as suggested in this paper, a study of the brain injury sustained may also yield further useful information.

It is estimated that at the present time not more than a third of motor-cyclists over the country are wearing helmets. Every encouragement should be given to motor-cyclists to wear them. The Government could give a useful lead by removing the remaining purchase tax from these helmets. It should not be supposed, however, that this would be by any means the complete answer. The relief of a few shillings is unlikely to influence a young man who is prepared to pay a high price for a modern machine. Indeed, cost is rarely given as a reason for not wearing a helmet. The usual comment is that they are too hot or uncomfortable, or give rise to an unpleasant drumming in the ears. We rather suspect the real reason to be in many instances that a helmet detracts from the freedom and verve of riding an open machine. The motor-cyclist needs to be assured of the value of a crash helmet, and work should continue to produce a cheap, comfortable, and efficient helmet ready for his use. Parents and employers, motor-cycle clubs, and "ace" riders can all help to encourage and popularize their use.

Summary

The problem of head injuries in motor-cyclists and the use of crash helmets is discussed, based on 555 civilian motor-cyclists and 135 Army motor-cyclists admitted to two hospitals in recent years.

Of all head injuries due to road accidents, 30% occur in motor-cyclists. Although the mortality from head injury due to all causes has fallen in the last seven years from 12.3 to 4.3%, the proportion of deaths among motor-cyclists has risen from 26 to 37%.

The findings among the injured motor-cyclists wearing crash helmets are described. The wearing of an efficient helmet leads to a significant reduction in the risks of severe and complicated skull fractures. Illustrative examples are given of the particular value of helmets in various circumstances and the criteria of an effective helmet are outlined.

Not more than one-third of motor-cyclists wear crash helmets at present—all should be encouraged to do so.

Our thanks are due to the Road Research Laboratory, Harmondsworth, Middlesex, and to the War Office for their helpful co-operation at all stages; to Mr. E. Tugwell for the photographs; to Sister B. Twining and Miss Sheila Nicholson for their help in the analysis of the records; and to Mr J. C. Scott and Mr. Joe Pennybacker for their helpful advice.

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MYASTHENIA GRAVIS

A PERSONAL STUDY OF 60 CASES

BY

HUGH GARLAND, T.D., M.D., F.R.C.P.

AND

A. N. G. CLARK, M.D.

Department of Neurology, General Infirmary at Leeds

Reference to standard textbooks provides contradictory statements about the early observations on myasthenia gravis. The first recorded example may well be that of Thomas Willis (1672). Gowers (1877), Erb (1879), and others recognized a form of bulbar palsy that clearly did not result from "progressive muscular atrophy" (motor neurone disease), and had noticed the absence of histological changes in the central nervous system; but of the earlier writers the greatest credit should perhaps be given to Jolly (1895), who first used the term "myasthenia gravis pseudoparalytica." He described two cases and referred to some 17 others in previous medical writings (11 of these 19 patients had died); he described the myasthenic reaction to electrical stimulation of muscles, and was the first to draw a parallel between the symptoms of this disease and those produced by certain alkaloids. He went further, and suggested the use of physostigmine in treatment, and, although regarding this as potentially dangerous, came within an ace of achieving the most important therapeutic advance, which was not to be made for another forty years (Walker, 1934). Prior to 1934 there was no treatment of value and the mortality was certainly very high.

Since 1895 very little has been added to the clinical picture, and the basic aetiology remains completely obscure, though some aspects of the underlying biochemical disturbance are now understood (Viets and Gammon, 1955). There have, moreover, been remarkably few studies of personally observed patients over a long period, and in Great Britain, excluding the

highly selected groups subjected to thymectomy by Keynes (1949, 1954), the first of such observations seem to be those of Ferguson, Hutchinson, and Liversedge (1955).

Morbidity

As is usual with morbidity figures, the real incidence of myasthenia gravis in any country is unknown. There are several reasons for this. An incorrect diagnosis is often made, chiefly in the milder examples, and particularly when presenting symptoms are solitary, as with diplopia or vague "weakness." In our own experience more severe and long-standing cases, with widespread symptoms and serious disability, have been regarded as suffering from disseminated sclerosis, and general and even severe "weakness" is not infrequently regarded as neurotic. Even if it were possible, therefore, to discover the frequency with which the diagnosis had been made in a known population at any one moment there would always be a number of undiagnosed or incorrectly labelled examples. Some generalizations may, however, be of interest. Personal experience suggests that where a neurological opinion is available most patients sooner or later reach the neurologist.

The present review is of 60 patients observed by one of us (H. G.) in 15 (interrupted) years of civilian private and hospital practice, and traced as far as possible from 1934 to September, 1955. One of these was a visitor from a foreign country and two were from another county; the rest, at the time when seen, were resident in Yorkshire, and probably were drawn from a population of about 3½ million. That all examples from this population would not be seen by one individual is obvious, and is made clear by a breakdown on a geographical basis. Of the 57 domiciled in Yorkshire 18 lived within the city of Leeds, with a population of about 500,000; at the time of writing 13 are alive and resident in the city, an incidence of about 1 in 40,000. There are 44 known to be alive in the rest of the area served by the Leeds Regional Hospital Board (which is the greater part of Yorkshire), giving an approximate incidence of 1 in 80,000. The incidence in Great Britain is certainly greater than 1 in 40,000, suggesting that there are at least 1,500 victims in the whole of the country. R. S. Schwab (1956, personal communication) has estimated the incidence in the U.S.A. at 30,000, making a very generous allowance for unrecognized examples; this is a sharp increase on the figure of 1,500 estimated by Viets (1948). The figure for Great Britain comparable to that of Schwab would be about 10,000, but we believe that the incidence is much less than this.

The present series bears a striking numerical resemblance to that of Ferguson *et al.* (1955); in their series 85 patients were seen in the continuous period 1932–54, coming from a population of about 4½ million; of these, 80 had been seen by one neurologist (F. R. Ferguson, 1956, personal communication). Although the annual number of new patients seen by us varied from 0 to 10 the average was 5, and this was the actual figure for the first and the last year under review; this incidence of five new patients per annum was also the experience of Ferguson.

Another comparison is with the estimated incidence of Parkinsonism in Great Britain of about 27,000 (Garland, 1952); in the private practice of one of us (H. G.) in the period under review 200 examples of Parkinsonism were seen and only 15 of myasthenia gravis, and this would suggest an approximate incidence of myasthenia in Great Britain of about 2,000.

Analysis of Case Material

Of the 60 patients under review, 7 could not be traced in 1955, and of these 5 had been seen prior to 1938; much of the information therefore relates to 53 patients.

There were 35 women and 25 men. The age at onset of presenting symptoms ranged from 6 to 75 years. In 40 (65%) symptoms first appeared between 21 and 50, and 3 (all women) had their first symptoms over the age of 65. The shortest duration (with a fatal issue) was one year and the longest history of continuing symptoms 28 years. Table I shows the age of the patients at the onset of symptoms. The figures do not seem to confirm the conclusions of Schwab and Leland (1953) that the onset is twice as common in young females as in young males and twice as common in old males as in old females; about 30% of both males and females had their first symptoms under the age of 30, as opposed to Schwab and Leland's figure of about 30% and 60% (their series related to 367 patients).

TABLE I.—*Age of Patients at Onset of First Symptoms*

Age	Male	Female	Total
1–10 years	0	1	1
11–20 ,,	3	3	6
21–30 ,,	4	8	12
31–40 ,,	7	7	14
41–50 ,,	4	11	15
51–60 ,,	7	2	9
61–70 ,,	0	1	1
71+ ,,	0	2	2
Total	25	35	60

Signs and Symptoms.—The duration of the illness before a diagnosis was established showed the wide variation of one week to 20 years, though in more than a third symptoms had not been present for more than six months. Table II is an analysis of the commoner clinical manifestations: these are arbitrarily classified as "early" if they occurred in the first six months, or "later." In Table II the incidence of "early" manifestations is accurate, but the second column is incomplete because of the seven untraced patients. Of the rest (53), 12 had had only ocular manifestations at the time of writing (about 25%) as compared with Ferguson *et al.* (1955), whose figure was 27 out of 75 (30%). Conversely, only 5 of the 53 had at no time complained of ocular symptoms. Thirteen had had symptoms for four years or more before the diagnosis was made, and eight of these had complained of intermittent diplopia only. Of 26 with ocular symptoms at the beginning of the illness only three developed other manifestations of the disease after a year, the longest interval being three years; this lends some weight to the suggestion of Grob (1953) that if myasthenia gravis results only in ocular manifestations for one year or more other disabilities are unlikely to appear.

TABLE II.—*Onset of Commoner Clinical Manifestations in* 60 *Patients*

	Early	Later	Total
Diplopia	36	13	49
Ptosis	26	14	40
"Asthenia"	21	4	25
Weakness of arms	12	13	25
,, ,, legs	14	12	26
,, ,, jaw	6	6	12
,, ,, neck	4	3	7
Dysphagia	8	11	19
Dysarthria	11	8	19

Methods of Treatment

Medicinal

To those who can remember the pre-"prostigmin" days it is now clear that this drug (a synthetic compound closely allied to physostigmine) has completely changed the outlook for the myasthenic; whether the same can be said of thymectomy is by no means as certain. (The drug was originally known as prostigmin and is still familiar to most practitioners by this name; it is, however, now officially known as neostigmine *B.P.*, which will be used in the rest of this paper.) There is no rigid dose of neostigmine, in which respect it might well be compared with insulin in the treatment of diabetes; each patient is given as much as he needs to control his disability. Although 600 mg. daily (40 15-mg. tablets) is not infrequently quoted

as a maximal dose, four patients in this series have taken 1,000 mg. a day, or more, sometimes for long periods, and one has had an average daily dose of 600 mg. for nearly 20 years. It is our practice to let the patient discover the optimum dose by personal trial.

Although abdominal symptoms (including vomiting, diarrhoea, and colic) are not infrequent in the early stages of treatment, they tend to disappear within a few months even with increasing dosage; the absence of such abdominal symptoms in those on massive dosage is probably diagnostic of myasthenia gravis. We have rarely found it necessary to give tincture of belladonna, though this occasionally controls the troublesome side-effects. The patient soon becomes the best judge of total dosage and of spacing; it is unusual to take more than 10 tablets (150 mg.) at a time or more frequently than every two hours. Many prefer to take the drug with meals or with milk. We have not seen any evidence of overdosage, though this possibility has been stressed by Schwab and Timberlake (1954). When symptoms are not fully controlled by neostigmine we have not been impressed by the effects of additional drugs, such as potassium salts or ephedrine; our personal experience of the newer drugs tetraethylpyrophosphate (T.E.P.P.) and pyridostigmine ("mestinon") is too small to be of significance.

Irradiation

Seven patients were treated by *x*-irradiation to the thymus. This is a more popular therapy in the United States than in Great Britain, and its use in this series has admittedly been capricious. With the exception of the 40 patients described by Grob (1953), there seems to have been no sizable series of patients treated by this method and compared over a long period with a similar series treated medicinally, and this appears to be equally true for the operation of thymectomy. Keynes (1954) discussed the use of irradiation in combination with operation in those examples of myasthenia associated with *x*-ray evidence of thymic tumour. One of our patients is worthy of mention; he was dependent on 750 mg. of neostigmine daily, but within a few months of irradiation the drug was completely withdrawn and he has remained symptom-free for over five years; no conclusion, however, can be drawn, because a complete and "spontaneous" remission of this duration falls well within the known natural history of myasthenia gravis. Of the other six patients, two subsequently died of myasthenia, two were in no way affected by the treatment, and the others have been observed for only a few months. Irradiation has the merit of being apparently completely harmless.

Thymectomy

Only six patients were subjected to thymectomy, between the years 1943 and 1950; five of these operations were carried out in the Department of Thoracic Surgery at the Leeds General Infirmary, and one, having first been seen by us, was later subjected to operation by Sir Geoffrey Keynes. None of the five operated on in Leeds had a thymic tumour. This is clearly too small a series from which to draw any conclusions on the value of the operation, but there is no evidence that thymectomy helped any of these six patients; at the time of writing four are still dependent on large doses of neostigmine, and the remaining two were similarly dependent for the first three post-operative years. The course of all six following operation has fallen well within the natural behaviour of the disease, and the fact that all six are still alive has probably no statistical significance. According to current American thought (Eaton and Clagett, 1955), the indications for thymectomy are considered to be that the patient should be a female, under the age of 50 and with a history of myasthenia of not more than 10 years and with no evidence of thymoma. Three of these six patients fulfilled these criteria, but in them the operation appears to have been ineffective; only one (in the whole series) fulfilling the above criteria is known to have died of myasthenia gravis within the thymectomy era.

Mortality

Of 53 patients who can be traced, 9 have died from myasthenia gravis. Of these, 5 were females and 4 were males, and at the time of death the youngest was 21 and the oldest 62. The history of myasthenic symptoms varied from 7 months to 13 years, and the duration of neostigmine therapy at the time of death was from three months to seven years. Seven are recorded as having had bulbar symptoms and dyspnoea during the course of their illness. In this disease bulbar symptoms may always be of serious omen, and dyspnoea invariably calls for immediate admission to hospital. Grob (1953) and Randt (1953) have shown that even with severe respiratory paralysis patients can be kept alive by modern methods of artificial respiration, with eventual improvement.

We do not know whether the remaining seven patients are alive or dead; at the time of writing, the mortality of this series of 60 patients, therefore, lies between 9 and 16 (15 and 25%). The comparable figure for the Manchester series was not specifically stated, and the figures in the table and conclusion 1 in that paper are a little misleading (Ferguson *et al.*, 1955). The facts relating to mortality in their series appear to be as follows: of the 85 patients under review 15 were known to be dead at the time of writing, but 3 of these had died of unrelated conditions, and the cause of death in another was unknown. Six of these deaths resulted from myasthenia gravis, but the patients had been subjected to thymectomy and were considered separately from the medically treated group. Six other patients were untraced. It would therefore seem that the mortality from myasthenia gravis in the Manchester series of 85 patients was not less than 11 or more than 18 (13–21%) at the time of writing, with 3 further deaths from unrelated conditions.

Because many patients are not incapacitated by myasthenia if it is mild, is in a phase of natural remission, or is controlled by the use of neostigmine, Ferguson *et al.* (1955) suggest that the adjective "gravis" is not always applicable, but since the mortality seems to be not less than about 20% and it is quite impossible to forecast the future for any patient, at any stage, with any degree of accuracy, we feel that myasthenia is still well termed "gravis."

Remissions

"Spontaneous" remission of symptoms is one of the characteristics of myasthenia gravis, but "remission" in this disease needs further qualification. Quite apart from the effects of treatment, the severity of symptoms varies from day to day, in addition to the characteristic tendency for disability to increase towards the evening. This natural fluctuation is reflected in the very variable dose of neostigmine necessary, in any one patient, for the control of symptoms. These variations might be called partial remissions, and it is this aspect of the disease which makes the assessment of such forms of treatment as thymic removal and irradiation difficult. But such partial remission merges into the more vivid picture of total "spontaneous" remission, in which the patient with the most severe disability may suddenly return to normal and remain so for a period known to be as long as 29 years (Eaton *et al.*, 1949).

The complete history over the whole course of the disease up to the time of writing was available in only 48 patients, of whom 24 had not had a complete remission. The remaining 24 had had periods of freedom from symptoms ranging from days to seven years, during which no treatment was necessary.

Contemporary Assessment of the Series

In a disease with such mercurial behaviour as myasthenia gravis assessment at any given moment must be unreliable. Table III shows the present position and is probably an average approximation. It will be realized that a patient in group 1 to-day may be in group 4 at any moment, and the reverse is equally true. It may be noted that of 44 patients

15 are in complete remission and not taking neostigmine at the time of writing, and 9 others (a total of 24, or 55%) have transient or minimal ocular symptoms only.

TABLE III.—*Contemporary Assessment of the Series*

Group 1 (minimal or no disability)	24
„ 2 (slight disability)	13
„ 3 (moderate „)	7
„ 4 (severe „)	0
Dead	9
Not traced	7
	60

Group 1=Normal activity with minimal, transient, or no ocular symptoms. Group 2=Slight tiredness or more prolonged ocular symptoms. Group 3=Unable to work or do housework but still ambulant. Group 4=Bedridden, in hospital, or unable to walk.

Summary

Myasthenia gravis is an uncommon disease, but its incidence is at least 1 in 40,000 of the population, and there are probably at least 2,000 examples in Great Britain at any one time.

The records of 60 patients (25 males and 35 females) personally observed over the period 1934–55 have been analysed.

The age of onset of symptoms varied from 6 to 75 years, being between 21 and 50 in 65%.

The diagnosis is frequently overlooked in the early stages, especially when there is a monosymptomatic onset.

Twelve patients had purely ocular symptoms throughout; conversely, in only five was there no history of ocular symptoms.

The disease is characterized by daily fluctuations as well as by partial and complete remissions, sometimes for long periods. In this series 50% at no time had had a complete remission.

The shortest history in a fatal example was one year. The longest history of continuing symptoms was 28 years.

The discovery of neostigmine has revolutionized the treatment and prognosis of the disease; very large doses can apparently be taken for an indefinite period, the highest dosage in this series being 600 mg. a day for 20 years. Personal experience of other methods of treatment (including thymic irradiation, thymectomy, and the use of pyridostigmine) is too small from which to draw conclusions.

The mortality in medically treated patients is still probably not less than 20%.

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The Government of Iraq has notified the World Health Organization of its intention to contribute a sum of $4,200 to the World Fund for Malaria Eradication. This is the fourth contribution to this voluntary fund, previous gifts having come from Brunei, China, and the Federal Republic of Germany.

ROLE OF VITAMINS IN EMBRYONIC DEVELOPMENT

BY

D. H. M. WOOLLAM, M.D., M.R.C.P.

AND

J. W. MILLEN, M.D., D.Sc.

From the Department of Anatomy, Cambridge

The therapeutic value of vitamins has been the subject of some scepticism in recent years. To some extent this represents a normal and healthy reaction to the extravagances of the immediate pre-war period when, as Christian (1947) put it, there arose "between the clinic and the advertising world . . . an hysteria about vitamins and other factors of nutrition with many wild statements often not properly restrained by those with medical training." It is now generally recognized, however, that the vitamins are not drugs to be abandoned because they fail to cure certain diseases; they are essential food factors, and unless they are present in our diet we die.

Requirements during Pregnancy

During certain periods of life there is an increased demand on the part of the body for vitamins. The most important of these periods is pregnancy. From the original observations that beriberi and night blindness occurred more commonly in pregnant women, it has gradually become recognized that there is an increased requirement for all the vitamins during pregnancy. Some obstetricians are even inclined to attribute some of the common disorders of pregnancy, such as uterine haemorrhage, to vitamin deficiency (McIlroy, 1935). Be that as it may, in recent years the supplementation of the diet of the expectant mother with an adequate supply of vitamins has become a recognized feature of antenatal hygiene. There is a possible danger that, with the increasing scepticism concerning the value of vitamins, this precaution may cease to be taken.

The tendency has been for apologists for the administration of vitamins during pregnancy to stress the significance to the mother of hypovitaminosis at this critical time. A great deal of work has now been performed which shows that, in experimental and domestic animals, an adequate supply of vitamins is of the utmost importance to the developing embryo. This side of the picture has been somewhat neglected, and it is the object of this paper to draw attention to what may happen to the developing foetus if its mother is not in receipt of an adequate supply of vitamins, or is in a state of vitamin deficiency when she conceives.

A vitamin deficiency can affect the foetus in two ways, depending on the stage of embryonic development at which its effects are felt. During the early period of pregnancy a single fertilized cell changes into a complex multicellular organism. In this "period of differentiation" the various organs are built up to what is virtually the adult pattern. The later period of pregnancy is devoted to growth in size, and this growth continues without a break after birth. Generally speaking, therefore, the effect of a vitamin deficiency during the first stage (corresponding to the first three months of pregnancy in the human) will be to interfere with the development of vital organs, such as the heart and the brain, which are then in a critical stage of their development. The result will be the birth of a foetus with a congenital malformation which represents a form of arrested or abnormal growth. If the effect occurs in the later period of pregnancy it will fall on tissues which behave as do those of the adult, and if any lesions are produced they