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THE RESULTS OF THYMECTOMY IN MYASTHENIA GRAVIS*

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It is now eight years since the treatment of myasthenia gravis by thymectomy was first described by Blalock, of Baltimore, and seven and a half years since the first thymectomy for myasthenia was performed in this country. The experiment was initiated by Dr. Arnold Carmichael and his former assistant, Dr. James Carson, and I am proud to say that it was to my hands that they entrusted the performance of the first operation. This was at New End Hospital, in association with Mr. J. E. Piercy, in February, 1942, and the experiment has flourished to such an extent that we have now operated on 155 myasthenic patients, and a considerable number of operations have also been done by other surgeons in this country. It may be admitted, therefore, that enough patients have been treated and a long enough time has elapsed for it to be possible to survey the results in such a way as to form a true idea of the value of the operation, both in its immediate and in its remote effects.

A difficulty in the way of assessment of results is immediately encountered in the well-known tendency of myasthenia gravis to show "spontaneous remissions" of symptoms, for it may be said (and it has been said on several occasions) that the effect of operation, if it seems to be beneficial, may be really no different from what might have occurred spontaneously. It is necessary, therefore, to show that post-operative remissions are both more frequent and more prolonged than could have been expected in the course of nature. It will not, I think, be very hard to do this. First, we must get some idea of the remission pattern in a series of patients who have not had surgical treatment, and here we find help in a paper published last year by Professor A. M. Harvey (1948), of Johns Hopkins University.

He first reviewed a series of 87 patients published by Kennedy and Moersch in 1937. Twenty-seven of these patients had complete remissions, ranging from one month to 16 years; but the majority lasted less than one year, and the average was only 2.2 years. Some of these supposed "complete" remissions were probably, in fact, only partial. Of Professor Harvey's own series of 125 patients, 17 had significant clinical remissions, nine of which lasted over two years. Only one lasted over five years. Professor Harvey has noticed that since the introduction of neostigmine ("prostigmin") therapy spontaneous remissions have been less enduring, and that only one patient so treated had a remission of over two years. This observation is important, because practically all the patients in our series had had neostigmine therapy before operation, and if Professor

Harvey is right an insignificant proportion of them would have had lasting remissions. Clearly it would be absurd nowadays to withhold neostigmine therapy on the chance of a few patients having spontaneous remissions. All, or practically all, will have had neostigmine, and the probable incidence of spontaneous remission lasting more than two years would be extremely small.

Four Categories of Results

I have referred on other occasions to the difficulty of assessing results in a disease so extraordinarily variable as myasthenia gravis. In my first communication (Keynes, 1946a) the patients were divided into the four following categories according to results, and the same method is still adopted: (A) Quite well; no symptoms; no neostigmine. (B) Virtually well; minimal symptoms; small dose of neostigmine. (C) Some improvement, often considerable; neostigmine still necessary. (D) No change.

Before considering the numbers that we have placed in these four categories it is necessary to emphasize that those patients who have been found to have thymic tumours have been excluded. The course of the disease and the effect of operation in these patients have been so different from the others that we believe a truer view of the value of operation can be obtained if we first consider only those who were free of tumour formation. Tumours can now nearly always be diagnosed by radiology before operation is undertaken, so that these patients can be set aside for a different plan of action; they therefore form a group for separate study. The incidence of tumours has been found to be 11.6% of all patients, so that the number of patients remaining for assessment is still satisfactory after this deduction has been made.

Patients have been carefully followed up, a few necessarily only by post, since they live in distant parts of the country or in the Dominions. The great majority have been seen personally, and not only by me and by my surgical colleague, Mr. J. E. Piercy. Patients at Queen Square have been seen by Dr. Carmichael and other members of the staff; those at New End by Dr. Raymond Greene; and those at St. Bartholomew's by Dr. Aldren Turner and Dr. Scowen. The number of patients treated privately has been insignificant.

The number of patients available for assessment, after deducting the post-operative deaths (10), the tumours (18), and the few that have not yet been assessed (7), is 120.

The figures for the four categories described I find to be as follows:

(A) 39 (32.5%)	(B) 40 (33.3%)
(C) 31 (25.8%)	(D) 10 (8.3%)

*A lecture given at the National Hospital for Nervous Diseases, Queen Square, on July 7.

Operative Mortality

The results of the operation can naturally be assessed only among those who have survived the operation—though death is unfortunately one of the possible results, and this must be carefully considered. The total number of patients who died as the immediate result of the operation is 10, but a high proportion of these deaths occurred during the early stages of the experiment, when experience of the operative technique and of the management of patients was small. This is reflected in the fact that five deaths occurred among the first 18 patients and only five in the next 119 operations. If it is fair to take this long consecutive series as the basis, then 4.2% represents the present operative mortality in experienced hands. This is a low figure considering the relatively poor human material with which we have to deal, for myasthenic patients with their narrow margin of respiratory efficiency are unfavourable risks.

The cause of death may be attributed in almost all instances to pulmonary complications; in none, so far, to loss of blood at the operation or afterwards. The pulmonary complications have been occasionally those of an acute myasthenic crisis in which the patients drown in their own secretions; more often they have been attributable to atelectasis of part of a lung or to a flare-up of a pre-existing bronchitis. The risk is always greater in the older patients and in those with coexisting disease—and it is of course the older patients who tend to have the coexisting disease. Thus our death roll included a man of 37 with chronic alcoholism, a woman of 46 with rheumatoid arthritis and cardiac degeneration, and a man of 47 with thyrotoxicosis and cardiac degeneration. Whenever a pulmonary infection becomes established a vicious circle tends to follow, since any acute infection in a myasthenic patient tends to make the myasthenia worse and the response to neostigmine less complete.

Moreover, in the early part of the series we were learning, through experience that was sometimes bitter, how best to perform the operation and how to steer a myasthenic patient through the post-operative period. Before February, 1942, no one in this country had ever performed a total extirpation of the thymus gland. Knowledge of its anatomy was hazy, and some of the information regarding its natural history was erroneous. Blalock's first communication gave very little technical help, though it emphasized the necessity for giving the patients an intravenous drip after operation.

Improvement in Technique

I am not now concerned with details of technique, but naturally our handling of the thymus did improve with experience, and soon it became obvious to us that the prime necessity was to keep the patients dry. To give an intravenous drip to a patient who had not lost a great deal of blood, and who did not suffer from much surgical shock, was unnecessary, and in a patient who tended anyway to produce an excessive bronchial secretion it was actually pernicious. As technique improved we realized the importance of removing the thymus without injury to the pleura, since even temporary collapse of a lung is harmful to a myasthenic patient; also it is easier to ensure pulmonary efficiency if the pleura has not been opened than after any transpleural operation or after accidental opening of the pleura, which may be difficult to close. Nevertheless we still have occasional arguments with thoracic surgeons, who are so accustomed to transpleural operations in non-myasthenic patients that they do not yet appreciate the extra dangers introduced by the presence of myasthenia.

Another strange fact that not all physicians seem to know is that it is dangerous to give a myasthenic patient an enema. Almost invariably the patient will collapse with syncope. This sounds improbable, but we do not doubt that it is a real danger. Early experience on several occasions had warned us, but we had not seen it happen for a long time and had almost come to disbelieve it. We tried to ensure, however, that the ward sisters had fully warned everyone concerned. On one occasion recently the warning, though given in writing, had failed to register. An enema was given, and the patient became unconscious and pulseless. We hope that the experiment will never need to be repeated.

I have referred already to the myasthenic crisis characterized by excessive bronchial secretion, sometimes followed by pulmonary consolidation and death. Occasionally death may be due to a more suddenly fatal cause—complete failure of both heart and respiration.

In April, 1948, a girl aged 16 had travelled from Singapore to London for thymectomy to be performed. Six months previously she had developed symptoms of myasthenia, first noticed as weakness of the arms when brushing her hair. Later the symptoms were mainly bulbar, but varied greatly in severity from time to time. On the voyage to England she had several attacks of dyspnoea, which greatly alarmed her. An operation done in July, 1948, was no more than a skin incision and exploration with a finger in the mediastinum, because at this stage the presence of a tumour was suspected, and the incision was closed. She was then given a course of deep x-ray therapy to the thymic area. This had to be stopped half-way through because she became much worse, but it was afterwards completed, and ultimately she greatly improved. She increased in weight and became transformed in appearance, so that the next operation was undertaken with great hopes in December, 1948. A somewhat shrunken thymus not showing any obvious tumour was removed without difficulty and the girl was not immediately affected by the operation. Within two hours, however, there was a sudden failure of peripheral circulation, with extreme pallor. Respiration then ceased and she died in the course of a few minutes. Those who were watching her said that the respiration seemed to stop an appreciable time before the heart had quite failed. At the post-mortem examination no adequate cause for her death could be discovered, and it could only be assumed that this was a form of myasthenic crisis following the disturbance of the operation.

This has been the only instance of death taking place so soon after the operation, and this kind of reaction is clearly exceptional.

The First Patients

Having these facts on the debit side of the account, let me now turn to the pleasanter side and give some account of the post-operative course of the patients who survived. First things come first, and so I must describe the first patient on whom we operated.

This patient was a woman aged 31 who had had symptoms of myasthenia for between three and four years. In February, 1942, she was a patient in the National Hospital, Queen Square, and her symptoms were very severe. Also they were getting worse, together with some mild signs of thyrotoxicosis, and it was thought that her prospects of survival were extremely bad. Thymectomy was therefore suggested, and this was done on February 10, 1942, together with a partial thyroidectomy. Her post-operative course was stormy, though on the fifth day she noticed improvement in nearly all her symptoms, and diplopia, present for several years, had disappeared. Nevertheless this same day she had a severe attack of dyspnoea with much mucus, and almost died. Ten days later she was almost completely well, and neostigmine was reduced to one tablet four-hourly with ephedrine. She had some temporary setbacks after this, but soon returned to her occupation as a land-worker, and has remained well to the present time—that is, for seven and a half years.

The second patient in the series had a thymic tumour and succumbed to the operation.

The third patient was one of the worst with whom we have ever had to deal. He was a man aged 34 who had worked in the National Fire Service. Symptoms of myasthenia had started nine months before we saw him, and had rapidly become worse until he was practically helpless, even with large doses of neostigmine. In addition he had a severe thyrotoxicosis with paroxysmal fibrillation. He was clearly going to die quite soon unless something could be done, and we judged that it would be best to deal with the thyroid gland first. A subtotal thyroidectomy was done on May 2, 1942, and his condition was critical for a few days, with rapid auricular fibrillation. However, he recovered, and after a month's interval a thymectomy was undertaken. He now had no symptoms of hyperthyroidism, but his myasthenia was worse, and he was extremely weak. The operation was done on June 15, 1942, and he stood it well. Some of his symptoms, such as those affecting the voice and swallowing, improved rapidly. The recovery of his skeletal muscles was slow, the delay being partly due to pronounced wasting of the muscles of his thighs and shoulder girdle. He was still taking a small dose of neostigmine two years later, but eventually was able to leave it off entirely, and for the last four years he has been quite well. It is now seven years since the thymectomy was done.

The next patient was a woman aged 44 with a six-years history of myasthenia. A thymectomy was done in May, 1942, and there was great improvement at first. Later she relapsed, and four years after the operation was much the same as before it was done. She died in 1947.

The fifth patient was a sailor aged 22 who had had symptoms of myasthenia for only 11 months, but he was already very ill, and without neostigmine was almost helpless. A thymectomy was done in May, 1942, and during the first 14 days he rapidly improved. A relapse then occurred due to an acute mediastinitis, probably following the liberal scattering of sulphanilamide powder in the mediastinum before it was closed (this was never repeated). Four weeks later he was without symptoms, and neostigmine was no longer given. Since that time he has been quite well.

It therefore seems that three of the first four patients who survived operation have had complete and permanent remissions if upwards of seven years is to be regarded as permanent. The evidence already given regarding the incidence of spontaneous remissions seems to make it unlikely that these recoveries were unconnected with the operation.

The Clinical Picture

Knowledge concerning the function of the thymus gland, whether normal or abnormal, is still very imperfect. We suppose that in removing the thymus we are getting rid of the source of a "curare-like substance" which is discharged into the circulation, though the final proof of this is still lacking. The histology of the gland in myasthenia shows that it is undoubtedly abnormal, and before long we hope to have some light upon the biochemistry of the disease; but even then we are unlikely to know why it is that results of thymectomy are so erratic. This uncertainty has discouraged some operators, including even Blalock himself, from advocating surgery. But the manifestations of the disease itself are just as erratic as the results of surgery, if not more so.

The clinical picture is never exactly the same in any two patients. There are great variations in the muscles affected and so in the mode of onset and in the course of the disease. It may first be noticed in the ocular muscles as diplopia—suddenly appreciated, for instance, during a game of tennis; in the levator muscles as ptosis; in the facial muscles, first noticed when applying lipstick; as difficulty in swallowing; or as weakness in the arms or legs. The disease may advance rapidly or slowly, or it may be

stationary for long periods. It may develop in a series of relapses, each being somewhat worse than the preceding one. This highly irregular pattern in the natural history of the disease is reflected in the effect of operation, but, provided that the results, taken broadly, are satisfactory, that is no reason for withholding operation.

Sometimes the effect of the operation is appreciated by the patient with an astonishing promptitude. I have known diplopia, present for years, disappear within 24 hours, never to return. Dysphagia is often abolished within a few days. Often within the first week the patient is aware of a new feeling of vigour in the limbs. The order in which symptoms disappear does not, however, obey any sort of rule. If generalizations are to be made, it may be said that ptosis and ocular palsies are usually the slowest features to disappear; sometimes ocular muscles remain permanently paralysed when all other symptoms have gone, and are then unaffected by neostigmine.

A patient who showed this in an extreme degree was a woman aged 24. She had a 19-months history of fairly severe generalized myasthenia with pronounced ptosis. A thymectomy was done in June, 1945. She made a good recovery except that the ptosis remained, and she afterwards went with her husband to Czechoslovakia. In 1947 she returned to England because, although neostigmine seemed to have some effect on the ptosis, she was unable to obtain the drug. When examined she had no symptoms of myasthenia except the ptosis, and neostigmine had little or no effect on this. She was accordingly given splints for her eyelids, and advised that she no longer needed neostigmine.

Although the ptosis is sometimes persistent, the other facial muscles usually recover well after operation.

In May, 1948, a patient from Australia who was in St. Bartholomew's Hospital gained widespread notoriety in the press as "the girl with the frozen smile." She was a girl aged 16½ with an eight-months history of severe generalized myasthenia showing complete immobility of the facial muscles. Her recovery after thymectomy was almost complete. She still takes a small dose of neostigmine, but her smile has been unfrozen, and this change took place within a fortnight of the operation.

Among those who have undergone complete recovery are a few individuals who are unable, for psychological reasons, entirely to give up taking neostigmine. Their dependence on the drug has over months or years induced a state of mind in which independence of it seems too good to be true, and they still believe it is necessary to take a tablet at irregular intervals, particularly in the evening, when normal fatigue is felt. The most extreme example of this was a girl who would take a tablet on Saturday evenings but at no other time. On inquiry it was found that this was preparatory to going to a dance. Examination of these people will not detect any signs of myasthenia.

It has been suggested by Professor Harvey (1948) that the administration of neostigmine might interfere with the effect of operation in the same way as it appeared to do with the occurrence of spontaneous remissions. In this connexion the following history is of interest.

A woman aged 37 was operated on in September, 1943. She had been the first patient to be treated in this country with neostigmine. She had had symptoms of myasthenia for 17 years, and had received neostigmine therapy for nine years. Though certainly better than before, she has not experienced very great benefit, and now, nearly six years later, she is still in category C.

Nevertheless a general survey of the results with special reference to the period of neostigmine therapy did not reveal any constant relation between them, and there is no justification for basing a prognosis on this evidence.

Failures

It will have been noticed that a small proportion of patients have not undergone any improvement at all. They have not necessarily been those who had severe symptoms of the disease or a long history.

A doctor aged 56 had mild myasthenia for one year, mainly affecting the movements of the lower jaw and lips. The thymus when removed in February, 1946, was quite large, though rather fatty in consistency. The patient's immediate response to the operation was excellent, and he left hospital a fortnight later without any symptoms of myasthenia. Nevertheless a month later he had relapsed to the same myasthenic level as before operation, and there he has remained ever since. He takes 45 mg. of neostigmine daily, with good response.

Another patient who failed to improve after a short history of disease was a man aged 47 who had myasthenic symptoms for two years, especially affecting the ocular muscles. His response to neostigmine was slow. After thymectomy, done in July, 1946, he improved a good deal and was able to return to work in a shop; but 18 months after operation he had relapsed to the same state as before.

A third failure was observed in a woman, aged 26, with moderately severe myasthenia of 15 months' duration. Thymectomy was done in January, 1947, and up to the present time she has not improved at all.

Nevertheless the average age of the failures has been nearly 40, including patients of 39, 41, 47, 56, and 61 years. The youngest was 26. Their histories have also tended to be long, including ones of 5, 8, 12, 12, and 20 years. Since, however, there were four others of 3 months, 1 year, 1½ years, and 2 years, clearly no general inference can be drawn at present. The number is too small for an average length of history in this category to have much meaning.

Age of Patient and Duration of Disease

When we examine the ages of the patients in the other three categories we find that A and B have a considerable proportion of patients of the age of 20 or below, whereas in category C only three are under 20. If the average ages in these categories are calculated, however, the differences are inconsiderable: (A) 28.3 years, (B) 28.4 years, and (C) 32.1 years. It seems, therefore, that the influence of age on the results is less important than at first appeared probable. On the other hand, the calculation of the average duration of the disease is more illuminating: (A) 2 years 2 weeks, (B) 5 years 4½ months, and (C) 7 years 7 months. Here the differences are very striking, and it seems clear that a long history is prejudicial to recovery after operation.

This confirms what I have stated in a previous communication (Keynes, 1946b). It seemed that on the whole the best results were obtained in patients with short histories and the worst in those with long histories, though it was seen that there were exceptions in both directions. It still remains true that the quickest and most complete post-operative remissions are to be expected after short histories, but as time passes it becomes plain that many of the long-history patients will ultimately give unexpectedly good results, although it may take longer to achieve them.

In November, 1948, I operated on two women of this type. One, aged 48, had been bedridden for 12 years; the other, aged 37, had not moved except in a wheel-chair for 27 years. After operation both improved slowly over several months, and, though their remissions are far from complete, both are now able to walk.

Many other patients with histories of five years or over have continued to improve slowly and have been upgraded from category C to B, or even to A.

Another long-term patient was a man aged 38 who, when first seen, had not yet been diagnosed as myasthenic. His appearance, however, was typical, and a test injection of neostigmine, to his surprise, established the diagnosis. He then admitted that he had crept through life only with difficulty, and that his condition had been much the same ever since he could remember anything. He afterwards produced photographs of himself at the ages of 2 and 4½ years, from which it was evident that he had been myasthenic since infancy. His history therefore covered almost 38 years, and when he came under observation he was getting steadily worse, with generalized and bulbar symptoms. He eventually decided to submit to thymectomy in September, 1947, and since that time has steadily though slowly improved. Now, nearly two years after operation, he still needs a small amount of neostigmine, but has been assessed as B, being able to lead a normal life.

Myasthenia Gravis in Infants

The history of this patient introduces the subject of myasthenia gravis in infants, which has specially engaged my interest since I was repeatedly told that the disease was unknown in children. A photograph of the last patient described showed him as apparently suffering from myasthenia at the age of 2; but this did not surprise me, because two years previously I had been asked by Dr. Wyllie to see a patient at Great Ormond Street Hospital for Children.

She was a girl of 4½, who had been admitted apparently moribund, with acute respiratory distress and cyanosis. An experimental injection of neostigmine had an immediate result, and it was then realized that she was suffering from acute myasthenia, symptoms of which had been present for at least a year. I removed the thymus in November, 1945, and she made a good recovery. A year later she still had mild symptoms, but was able to lead a normal life and was described as tireless.

Two months after this incident, which was the first of its kind ever known at Great Ormond Street, a child of 2½ was admitted in a similar state. She was cyanosed and helpless, and again was immediately restored by neostigmine. I operated on this child in February, 1946, and removed what I thought was the whole of the thymus gland. She made a good recovery, but it was only temporary. Four months later she had a severe relapse and quickly died. At necropsy a thymus gland was found equal in size to the specimen I had removed. It was evident that I had removed only one lobe of the gland and had failed to find the other—the only occasion, so far as I know, on which this has happened.

I have not seen another myasthenic infant since this date, though Griffith (1949) described an undiagnosed example. This child had died with symptoms exactly resembling those of the Great Ormond Street children, and it is probable that in the past many children have died of myasthenia, the true diagnosis not having been suspected.

Selection of Patients

Whenever the results of any operative procedure are rather better than preconceived ideas will willingly allow, the charge is made that there has been "selection" of patients. The implication is that unfavourable ones have been eliminated, so that the results seem better than they should be. In the present investigation there has admittedly been some selection of patients, but this has not been exercised by ourselves. It has been through the physicians that most of the patients have, very properly, come to the surgeons, and it is they who have made the selection, which has therefore been in the direction of providing unfavourable rather than favourable material.

Physicians have naturally hesitated to submit to operation patients with only the milder manifestations of myasthenia, such as diplopia, and especially those whose symptoms did

not seem to be progressive. On the other hand, they have not hesitated to recommend operation for patients who were seriously disabled by the disease or whose symptoms were becoming progressively worse. On the surgical side very little selection has been exercised, though a very few patients have been rejected on the ground that operation would clearly be fatal. Sometimes patients have been kept under prolonged observation in order to seize the opportunity of operating when the disease was in a favourable phase.

A patient recently admitted to St. Bartholomew's Hospital under Dr. Scowen had been myasthenic for 16 years. There had been periods of remission, usually partial, but on the whole the disease was progressing, and during the last six years had been very bad indeed. It was found that she responded well to injections of neostigmine, and in six years had had 24,000 of these, many given by her husband, who, being by profession a reader of meters, was accustomed to keeping records. Often the patient herself was too weak to reach for the syringe. She spent two months in Dr. Scowen's ward, and underwent some improvement in this period. When the moment was deemed favourable, the operation was done. This was on June 29, 1949, and she is now improving, the daily dose of neostigmine having been reduced from 270 mg. before operation to 180 mg. at the present time.

Dr. Arnold Carmichael has been so impressed with the results of operation that we have operated at his request on one patient who had no symptoms of myasthenia at all. This is not so odd as it sounds.

The patient, a girl aged 14, had had several attacks of myasthenia, with brief complete remissions between attacks. But Dr. Carmichael was satisfied that each attack was proving a little worse than the one before, and therefore asked for the operation to be done at the safest time—that is, during a remission. This patient has now remained well for six months since the thymectomy was done.

We have operated on one other patient during a remission. This was an Irish youth of 21 who had lost all confidence in himself owing to his relapses, though they were mild. He had developed a myasthenic mentality, which prevented him from following any occupation whatever. Now, two years after thymectomy, he has admitted that he is perfectly well, and he started to work some time ago. Such is the power of surgery over a work-shy neurosis even in a myasthenic Irishman.

It is unnecessary to emphasize the importance of a careful follow-up of thymectomy patients, as this applies to most diseases; but it is worth noting that with the passage of time the results after this operation tend to encourage both surgeon and patients. Many of them undergo a slow improvement over a long period, and very few show the opposite tendency. More patients therefore gain promotion in the ABCD classification than have to be put back, so that each time I have published results they have shown slight improvement on the time before. It must be admitted, however, that there are a few qualifications to be made. Even after apparently complete recovery some of the female patients find that there is a perceptible relapse at the menstrual periods. Secondly, both sexes, although their vigour is normal for ordinary exertions, sometimes find their strength is not completely restored for sustained exertion. It may be, therefore, that the Saturday evening tablet is not entirely psychological in its effect. Thirdly, there seems to be in some patients an irreversible change in one or more ocular muscles and in the levator of the upper lid, the movements being unaffected either by operation or by neostigmine.

Side-issues

It will probably be expected of me to say something on an important side-issue—namely, the relation of myasthenia

to thyrotoxicosis. Several writers have thought that there might be some such association, the belief being encouraged by the close anatomical and morphological relationship between the thyroid and the thymus, but we have not found any convincing evidence of this. Only four patients in the whole series of 155 have shown a definite thyroid excess, and in only one was it at all serious. Two of these patients I have already described. A third succumbed to the operation.

The fourth was a woman of 27 who was admitted to hospital with a diagnosis of thyrotoxicosis only, although soon after the onset of this in December, 1946, she had had occasional attacks of diplopia. Ptosis of the left eyelid followed, and then weakness of the left arm and both legs. The whole myasthenic picture then became more pronounced. Mr. J. E. Piercy performed first a subtotal thyroidectomy and then a total thymectomy. At the present time she is free of any symptoms of either disease on three or four tablets of neostigmine a day.

It has been pointed out by Dr. Raymond Greene (1949) that all the ocular muscles responded to neostigmine except the external recti, but that these steadily recovered after the thyroidectomy. The ocular movements therefore showed the mixed effect of myasthenic and thyrotoxic asthenia, each muscle responding to the appropriate treatment. Beyond this we have no evidence to offer. An incidence of four patients with thyrotoxicosis in 155 myasthenics does not seem to afford a basis for any conclusions, though it is perhaps somewhat higher than would be expected from mere probability.

Another side-issue which may be included among "results of operation" is the evidence concerning the supposed enlargement or persistence of the thymus gland in myasthenia. It has seemed to us that the size of the gland bears no relation to the severity or incidence of the disease. Apart from tumours the weight has varied from 3 to 36 g., the average being 15 g. It is now established that the thymus normally persists, and that it does not weigh more in myasthenic patients than in normal people of the same age, among whom the variation is just as wide. The only consistent abnormality has been in the microscopical appearance of the gland, as described by Bratton (1948) and Castleman and Norris (1949). This almost always shows conspicuous lymphoid "germinal centres"; these are not found in the thymus glands of other people.

Tumours of Thymus Gland

As I explained at the beginning, I have considered in the foregoing remarks only the results obtained in the treatment of patients who did not have thymic tumours. I do not now propose to deal in detail with those who had tumours, as they must be the subject of a separate study. It soon became obvious, however, that the presence of a tumour implied a very much worse prognosis. Patients with tumours usually have a short history and severe symptoms which respond slowly and imperfectly to neostigmine. The operation risk is increased by these features as well as by the greatly increased difficulty of removal. The immediate response to operation may be dramatic, but the patients tend to show after a short interval a serious relapse, and the symptoms become irreversible. They have usually soon died with respiratory failure. Primary operation has therefore been very unsuccessful in our hands. We now prefer to treat these patients with preliminary deep x-ray therapy, followed by extirpation of the thymus with the tumour if it is possible. A few patients treated in this way have given more encouraging results than those subjected to primary operation.

One patient who had a primary removal of a tumour in January, 1947, followed by deep x-ray therapy in June was slowly deteriorating, until Dr. Douglas McAlpine treated him with tetraethyl-pyrophosphate, since when he has steadily improved.

Conclusion

The treatment of myasthenia gravis by thymectomy has been called "empirical," and so it still is in the sense that there are a number of questions to be answered concerning the intimate details of the disease. The connexion between myasthenia and an abnormal thymus gland is now well established, but there is no clue to how or why the gland acquires its abnormal function. The chemistry of the secretion which is producing myasthenia is still quite unknown, and no active principle has yet been isolated.

Fundamental knowledge, such as the truth about the physiology of the neuromuscular junctions, is still lacking, so it is not surprising that understanding of abnormal functions is still defective. Surgery may help to provide an answer to these questions, which are far from being purely academic. In the meantime surgery, with the help of neostigmine, has undoubtedly made a practical advance in being able to alleviate the lot of many of the unfortunate sufferers from myasthenia gravis. There are few more pathetic sights than an otherwise perfectly healthy girl or youth reduced to a state of dependence and physical helplessness, and few more gratifying sights than their dramatic restoration to normal activity, a feat which surgery can now on many occasions claim to have achieved.

Summary

From February, 1942, to July, 1949, 155 patients with myasthenia gravis have been treated by surgical extirpation of the thymus gland.

Of 120 patients who did not have thymic tumours and survived the operation, 79 (65%) have shown a complete or almost complete remission of the symptoms. These could not be accounted for as "spontaneous remissions."

The operative mortality in our hands is at present 4.2%.

The results are influenced by the duration of the disease before operation: the shorter the history the better the results.

Early operation is indicated by the above fact, and by the 11.6% incidence of tumours, the development of which should, if possible, be anticipated.

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A statistical study by V. A. Fenger and J. Nielsen¹ shows that in the period 1908-15 the average duration of life of a Danish doctor aged 25 was 3 years shorter than that of his opposite number in the general population. In more recent years this difference has diminished considerably. This study, brought up to 1944, shows that the mortality among Danish doctors is lower than that among the whole population with regard to tuberculosis, cancer, and accidents. But it is higher with regard to suicides, and more than 40% higher with regard to heart disease. A comparison is made with the studies of Dublin and Spiegelman in the U.S.A., and a table is drawn up by the Danes showing how the Danish and American findings compare with each other in respect of each important cause of death.

¹ *Ugeskrift for Laeger*, June 30, 1949, p. 737.

INCIDENCE OF CROSS-INFECTION IN CHILDREN'S WARDS

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In 1945 the British Paediatric Association began to interest itself in the problem of cross-infection in children's wards in hospitals, and an *ad hoc* committee was set up to consider the matter. Its report was published in the *British Medical Journal* of May 4, 1946 (p. 673). During the committee's deliberations it became obvious that the views and experience of individual paediatricians differed widely. There was not only little information on the incidence of cross-infection but also little evidence of the effect of the common methods used to prevent or control it. The result was a report in very general terms "in the nature of a preliminary discussion," and the collection of evidence on the incidence of cross-infection and the evaluation of methods for its control were left for later investigation. This report is the result.

It is not easy to give an adequate definition of cross-infection in this context, but that suggested by the above-named committee was accepted and used—namely, "To denote any infection acquired by a patient in the hospital environment. Clinically, it is an infection arising during the course of another illness for which the patient was originally admitted to hospital, and may attack the respiratory tract, gastro-intestinal tract, wound, skin, or mucous membrane, or be manifested as one of the specific fevers." This definition places the final onus of diagnosis on the paediatrician, who may or may not have help from bacteriological investigation. This does leave room for a difference of personal opinion, but it was felt that experienced paediatricians would hold relatively uniform views, especially as nearly all those taking part in the investigation had preliminary discussions in committee with their colleagues.

The main objects of the inquiry were to determine: (1) the incidence of cross-infection in children's wards (nurseries for the newborn were excluded); (2) the effect of cross-infection on morbidity and mortality; (3) the part cross-infection played in increasing the length of stay in hospital; and (4) the methods used to prevent cross-infection and their relative efficiency.

Information Sought

Fourteen hospitals were selected as representing a cross-section of children's wards in which patients were under the clinical charge of an experienced paediatrician. The hospitals included examples of children's wards in a general hospital, wards in hospitals for children only, wards in teaching and non-teaching hospitals, and wards taking long-stay cases. In all, the records of 26 different wards were utilized.

Special cards were prepared and issued to each ward for recording the information in respect of every patient admitted. These asked for details of the age, sex, diagnosis on admission, how the child was disposed in the ward on admission and during its stay (e.g., bed in open ward, cubicle), and method of dispersal (e.g., transfer to another ward, transfer to isolation hospital, home). If cross-infection took place its date was to be noted, together with