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THYMECTOMY IN MYASTHENIA GRAVIS*

BY

HENRY R. VIETS, M.D.

*Neurologist, Massachusetts General Hospital, Boston ; Lecturer
on Neurology, Harvard Medical School*

In reporting four years ago (Viets, 1945) on the effects of thymectomy in our first 15 patients subjected to this operation, I stated that the procedure was "still in the experimental stage, with slight but definite indications, however, that there is some relation between the thymus and myasthenia gravis." I find myself in practically the same position to-day, with more than double the number of cases to evaluate and a considerable augmentation of the literature on the subject, with case reports from other clinics, some larger than mine. The evidence of thymic involvement in myasthenia gravis is still present, and relatively unchanged ; added experience has only confirmed my opinion of 1945. All cases here reported have been observed in my clinic for many years and have been operated upon by the surgeons of the Massachusetts General Hospital staff. Examinations of the thymic tissue, freshly removed at operation, have been made by the hospital pathologists. Each patient not surviving operation, or dying later, with one exception, has been examined at necropsy. Although the series is small, cases have been carefully controlled, both before and after operation. The condition of each patient is known as the result of personal observation.

NON-NEOPLASTIC THYMUS SERIES

Of the 36 patients with myasthenia gravis treated by thymectomy from 1941 to August, 1949, seven with thymoma are considered later. Four of the 29 with non-neoplastic thymuses at operation have died, three being consecutive operative deaths in 1943 (Cases 9, 10, 11) and one (Case 30) a subsequent operative death.

Operative Deaths from Thymectomy (Four Cases)

Case 9

A husky water-front watchman, married, was first admitted on October 8, 1943, at the age of 31. He had developed dysarthria on extraction of a tooth, without procaine, nine months before admission. A week later, weakness of extension of the fingers, particularly the index finger, was noted, with increasing difficulty in raising mucus from the throat. In about six weeks the weakness became generalized ; he fell in the street and developed additional symptoms of dyspnoea, inability to smile or whistle, and unilateral ptosis. Five months after the onset of his illness he became suddenly cyanotic. Neostigmine, subcutaneously, was given with marked beneficial effect ; within an hour he felt like a "new man."

Course of Disease.—For the first five months after the onset, before the diagnosis, the patient had a relatively steady downward course. After the diagnostic test, which served as a therapeutic measure in a time of grave emergency, he was partially adjusted by 8 to 10 tablets of neostigmine (15 mg. each) in 24 hours, taken at intervals of two to three hours. The adjustment was far from satisfactory, for when I first saw the patient, four months after the treatment was begun, he showed weakness of the neck muscles, diplopia, ptosis, difficulty in holding his mouth closed and in chewing, inability to swallow solid foods, laboured speech, with nasal voice, and general muscular fatigue to such an extent that he could not run and even walking was troublesome. Owing to dysphagia his weight had fallen from 250 to 150 lb. (113 to 68 kg.) in a period of nine months. In hospital he continued to relapse. The oral neostigmine was raised to 24 tablets in 24 hours and a "booster" dose of neostigmine methylsulphate, 1 mg., was given subcutaneously. Although improved on this medication, he could not close his mouth firmly, smile, or talk without a nasal twang. A week in hospital brought him to a state of fair adjustment only, when thymectomy was done.

Thymectomy, October 16, 1943.—In order to maintain the patient during anaesthesia, 30 mg. of neostigmine methylsulphate and 3 mg. of atropine sulphate were added to 1,500 ml. of a 5% dextrose solution and given intravenously at the rate of 60 drops (3 ml.) per minute. Thus 3.65 mg. of neostigmine methylsulphate was delivered to the patient each hour. The entire 1,500 ml. was used in a period of slightly over eight hours. This medication was started half an hour before operation, and it was planned to follow the first eight-hour treatment with a second or third 1,500 ml. of the solution if advisable. Anaesthesia was induced by a gas-oxygen-ether mixture. Shortly after intubation, respirations ceased and artificial respiration was used from that point on throughout the three-hour operation. Thymectomy was accomplished through a midline sternal approach ; the thymus was removed without difficulty.

Pathology.—There was a moderate amount of involution. Germinal centres were seen in the medulla, but they were not numerous. The separation of the cortex from the medulla was not conspicuous.

Post-operative Course.—The patient was immediately put in a respirator and his condition was considered fair. Twelve hours after operation he was conscious and showed slight ability to breathe voluntarily, although he was still maintained in the respirator. Intravenous medication with neostigmine was continued. Two days after operation he was still being maintained on intravenous medication and artificial respiration. In spite of these measures he had a respiratory crisis usually every six to eight hours, associated with a large accumulation of mucus in the trachea and major bronchi. Some of the thick secretions were aspirated through a bronchoscope. This procedure was

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repeated on subsequent days, but bronchopneumonia, with pulmonary atelectasis and hydrothorax, developed and the patient died on the eighth post-operative day.

Necropsy.—There was a well-marked bronchopneumonia with pulmonary atelectasis of the left lower lobe and hydrothorax on the left.

Comment.—Prior to thymectomy an attempt was made to estimate the amount of intravenous neostigmine needed to maintain this patient adequately during the course of the operative anaesthesia and for a post-operative period of hours. After investigation it was estimated that he would require 30 mg. of neostigmine methylsulphate intravenously in a period of eight to nine hours. This proved to be in excess of the actual needs, and the excessive use of neostigmine may well have been a deciding factor in causing the cessation of respiration shortly after the anaesthesia was started and even the patient's ultimate death. The dosage used, given at the rate of 3,600 drops (180 ml.) an hour, delivered 3.65 mg. of neostigmine methylsulphate intravenously. Before operation the patient had been only moderately maintained on two 15-mg. tablets by mouth every two hours or 15 mg. of neostigmine bromide per hour. Subsequent investigation disclosed that a satisfactory formula was as follows: 15 mg. of neostigmine bromide taken by mouth is equivalent in effect to 0.5 mg. of neostigmine methylsulphate given subcutaneously or intravenously. This patient received about seven times this dose, or an equivalent of 105 mg. of neostigmine bromide by mouth per hour. The excessive secretions in the bronchial tree, as disclosed both clinically and at necropsy, plus the necessity for artificial respiration soon after the intravenous medication was started before the operation, indicated that the patient received more neostigmine than was desirable and that even the effect of the excessive dose was not overcome by additional atropine sulphate, given freely in the post-operative period by subcutaneous injection.

Three Other Cases

Of the other three patients who died operative deaths following thymectomy, two occurred immediately after Case 9 in 1943. At that time considerable difficulty was being encountered in adjusting the intravenous dose of neostigmine in order to maintain the patient adequately during the operation. The question of the proper anaesthetic for thymectomy was also being investigated. Before this time, gas-oxygen-ether mixture had been used by intubation, and it was often necessary to support the patient by artificial respiration during the operation, as in Case 9.

Case 10.—This patient, a married man, was first admitted on December 11, 1942, at the age of 62. He had had symptoms of myasthenia only one month before his admission to hospital. He was not a favourable case for operation, partly on account of age but principally because of arteriosclerosis. In August, 1942, he developed a right hemiplegia subsequent to a cerebral thrombosis. This had partially disappeared by the time he entered hospital. Intravenous neostigmine was not used during the operation. The same gas-oxygen-ether mixture was employed. The thymus was removed, but the pleura was opened on both sides and the right lung was punctured. The patient died of massive collapse of the right lung within 24 hours.

Case 11.—This patient, a single woman, was first admitted on November 22, 1943, at the age of 24. She had had symptoms of myasthenia gravis for four years, and at the time of admission she was well maintained on 10 to 12 tablets of neostigmine a day. She seemed to be a good subject for operation, and thymectomy was done in December, 1943. During the operation she was maintained on 1.5 mg. of neostigmine methylsulphate per hour, which would correspond to three tablets of neostigmine bromide. Anaesthesia was introduced by gas-oxygen-ether mixture. After operation the patient was still maintained on intravenous neostigmine, 1 mg. per hour. Subsequently she returned to oral neostigmine, but as this was not satisfactory the intravenous preparation was again instituted. She had a severe relapse of her myasthenia, but was immediately revived by intravenous treatment. Her condition was

precarious, however, for even when the intravenous therapy was stopped for a few minutes she had a myasthenic crisis. Difficulty was encountered in continued intravenous therapy after the third or fourth post-operative day, and the patient died of respiratory paralysis seven days after the thymectomy. The thymus showed moderate involution with a considerable number of germinal centres.

Case 30.—A married woman aged 49 was first admitted on January 6, 1949. She had had symptoms for about a year before admission, mainly ptosis and diplopia. She took neostigmine for three months before her thymectomy in January, 1949. She required a high dosage, up to 28 tablets a day, but was only fairly well regulated at the time of operation. Intravenous neostigmine was not used, but the anaesthetic was cyclopropane. Because of respiratory failure she entered a respirator on the first post-operative day and died suddenly of respiratory paralysis the next day. The thymus showed a moderate amount of involution and no germinal centres.

Comment on Cases 10, 11, and 30.—Death occurred immediately or within a few days after operation in each case. Presumably this was due to improper handling of the patients at the time of operation. Certainly this was so in the two cases that did not have the advantage of a properly adjusted amount of neostigmine given intravenously during the operative procedure. The initial dosage was incorrect and control was not maintained uniformly for a long enough period after the thymectomy. Cyclopropane anaesthesia was also an important factor in maintaining patients during the operative period. In two cases this drug was not used. Prolonged exploration may also be a factor in deaths from thymectomy. An effort to locate thymus tissue in areas above or below the usual field of exploration is justifiable provided it does not require a great extension of time. There are other technical factors, moreover, that make the operation hazardous, such as opening the pleura; but these are now controlled in most cases, and a long series of operations without fatality has been carried out since 1943, with the exception of Case 30 and a patient with a thymoma operated on in 1945 (Case 14).

Patients without Thymoma Surviving Thymectomy (25 Cases)

In the series of patients without thymoma there were 25 who were living in August, 1949: one had survived eight years (Case 1); three, seven years (Cases 2-4); one, six years (Case 7); two, five years (Cases 12 and 13); three, two years (Cases 16-18); eight, one year (Cases 19, 21-27); and seven, less than one year (Cases 29, 31-36). The cases may be divided into two groups: seven surviving five years or more and 18 surviving less than five years.

Patients Surviving Five Years or More (7 Cases)

Case 1.—This patient, a married man, was first admitted on June 23, 1939, at the age of 27. Thymectomy was done on December 5, 1941. Previous x-ray treatment over the thymic region had failed to give relief, but the patient was nearly free from general weakness on 14 tablets of neostigmine a day during a period of over two years before operation. His diagnostic test, equivocal at the onset, became definitely positive within a year. The thymus was partly involuted; there were a large number of germinal centres (Castleman and Norris, 1949, Case 14). After thymectomy the patient was still unable to work, and for eight years his symptoms have remained relatively fixed on an intake of 8 to 14 tablets a day. All the gain, estimated at 20%, was made in the first year after operation. The reason for his feeble response is not clear; other patients with a large number of germinal centres in the thymus have shown a more favourable reaction to thymectomy (Cases 16, 21, and 22). His improvement is classed as "poor to fair."

Case 3.—A married woman was first admitted on March 31, 1932, at the age of 22. Thymectomy was done on March 18, 1942, after more than 10 years of illness. During two pregnancies in this period she had an almost complete remission of symptoms, only to return to her previous level of myasthenia,

requiring about 12 tablets a day (Viets, Schwab, and Brazier, 1942, Case 1). X-ray treatment of the thymic region failed to influence the course of her disease. The effect of thymectomy was dramatic. Within two weeks all symptoms disappeared, and no medication has been required from that time for a period of over seven years of post-operative observation. The thymus was slightly involuted and showed numerous germinal centres, but not so many as in Case 1 (Castleman and Norris, 1949, Case 17). Her condition in August, 1949, was excellent.

The five other patients in this series (Cases 2, 4, 7, 12, and 13) showed no distinctive feature. One result was "fair," one "fair to good," one "good," one "good to excellent," and one only "poor to fair" (Table I). Age, sex, duration of disease, length

TABLE I.—Patients Surviving Five Years or More (7 Cases)

Case No.	Sex	Age at Onset	Years of Pre-operative Treatment	Age at Operation	Years of Post-operative Observation	Condition in 1949
1	M	26	2½	29	8	Poor to fair
2	F	13	4½	21	7½	Fair
3	F	21	6	32	7½	Excellent
4	M	30	5	35	7½	Good to excellent
7	M	18	1	19	6	Fair to good
12	F	18	1	19	5½	Poor to fair
13	M	33	6	46	5	Good

of previous treatment with neostigmine, x-ray treatment, and condition of the thymus at operation were factors that could not be correlated with the degree of improvement after thymectomy. It is of note, however, that *all patients were improved; none made worse*. The patient (Case 3) who was most favourably affected by her pregnancies was also most helped by thymectomy. She has the best record of any patient in the group surviving more than five years. Thus the endocrine aspects of myasthenia gravis are emphasized again, as they have been in the past.

Cases Surviving Less than Five Years

Of the 18 cases surviving less than five years, seven were operated upon in 1949, with their post-operative course too brief to be of value in estimating results (Table II).

TABLE II.—Patients Surviving Less than Five Years (18 Cases)

Case No.	Sex	Age at Onset	Years of Pre-operative Treatment	Age at Operation	Years of Post-operative Observation	Condition in 1949
16	F	29	3	32	2+	Good
17	F	24	1½	32	2+	Poor
18	F	21	2	23	2	Fair
19	F	27	2	29	1+	Excellent
21	M	20	2+	22	1+	Good to excellent
22	F	11	1+	13	1+	Fair to good
23	M	19	5	25	1+	Good
24	F	30	2	33	1+	"
25	F	29	5	36	1+	"
26	M	18	2	21	1+	Poor
27	F	17	4	22	1	Excellent
29	F	25	1	26	Months	Too soon to estimate
31	M	33	5	40	"	"
32	F	24	10	39	"	"
33	F	19	6	26	"	"
34	F	15	2	18	"	"
35	F	21	3	26	"	"
36	F	28	1	29	"	"

Five cases (Cases 17, 19, 21, 25, and 27) are chosen to illustrate the trends noted in the entire group of 11.

Case 17.—This patient, a single woman, was first admitted on April 1, 1946, at the age of 30. In 1940 she first noted intermittent double vision. She improved slightly, only to relapse in 1944 with nasal speech, ptosis, difficulty in swallowing, and regurgitation of liquids. A neostigmine test was positive and treatment was started in October. She was much better from October, 1946, to March, 1947, and was able to work part-time as a bookkeeper. She then relapsed, with increasing difficulty in swallowing, general weakness, "stiffness" of tongue and lower lip, and ptosis, and grew slowly worse, losing 40 lb. (18 kg.) in weight. She never responded well to medication despite careful regulation. On June 10, 1947, under

anaesthesia induced by cyclopropane, thymectomy was accomplished through a midline sternal approach. The thymus was removed without difficulty. There was marked involution, without germinal centres.

The immediate post-operative course was complicated by pneumo-hydrothorax. There was, however, an immediate response and the patient was able to reduce her intake from 12 to 7 tablets a day. This improvement continued for almost a year after thymectomy, when she began to relapse. She also had a tendency to respiratory infections, which always stimulated a relapse. Because of her continued relapse and lack of response and tolerance to increased dosage, the question of removal of further lymphoid tissue was raised. A splenectomy under cyclopropane was performed. When last seen in July, 1949, although her general strength seemed better, she still had difficulty in swallowing, nasal speech, ptosis, and diplopia.

Comment on Case 17.—The response to both thymectomy and splenectomy was unsatisfactory. Although some improvement was recorded immediately after operation, as is often the case, the gain was not held after the first year, and the general course of her disease was almost unchanged. Involution, at 32, had become so pronounced that the patient had largely thymectomized herself. In general, patients with marked involution of the thymus at operation have not had the most favourable results.

Case 19.—A married Chinese woman was first admitted on June 10, 1946, at the age of 28. She first noted difficulty in smiling and holding lips tense in September, 1945. Within two weeks her voice developed a nasal quality. In October, 1945, a diagnosis of myasthenia gravis was made. In January, 1946, she was unable to stand or walk because of the onset of leg weakness. A severe respiratory disorder developed requiring treatment in the respirator and hospital treatment for three months. Her weight dropped from 115 to 90 lb. (52 to 41 kg.) within a year. She was unable to comb her hair or put on a coat. While in the hospital she received x-ray treatment to the thymic region—600 r in all. Immediately after this her medication had to be increased but was soon reduced again. The rate of improvement was stationary for three months before admission for thymectomy. She had gained weight, was able to walk up three or four flights of stairs and to comb her hair, and she no longer had diplopia. Difficulty in swallowing was still present. She was moderately well maintained on five tablets a day. On November 13, 1947, under anaesthesia induced by cyclopropane, thymectomy was accomplished through a midline sternal approach. The thymus was removed without difficulty. There was a slight amount of involution of the thymus, with moderate to marked germinal centres.

The patient immediately did well post-operatively. She occasionally took two or three tablets a day if doing a lot of work. When talking for any length of time there was a tendency to a nasal voice, which was her only sign of the disease. She has continued to improve steadily and has been able to lead a normal social life. Her condition was excellent in August, 1949, nearly three years after thymectomy, when she was almost symptom-free.

Comment on Case 19.—The patient had a severe type of myasthenia gravis, with respiratory crises, requiring hospital treatment for months, tube-feeding, the respirator, and almost constant medication. She was as desperately ill as any patient in our series. By waiting for a favourable moment for operation, when the patient was well adjusted on a minimal amount of neostigmine, thymectomy was accomplished without difficulty. The operation was not one of "desperation," for the time was carefully chosen. In spite of her two-year pre-operative course, with a large neostigmine dosage required over many months, both by mouth (30 tablets) and by intramuscular injection, her response was excellent, nearly as good as that of any patient in our series. It should be remembered that this patient's illness since the start was characterized by spontaneous remission and relapses, some of several months' duration. No remission had lasted as long, or had been so complete, however, as her post-operative course.

Case 21.—A single Peruvian man was first admitted on February 12, 1948, at the age of 22. His first symptoms

occurred in July, 1946. Difficulty in using his lips was followed within a month by diplopia and weakness of bite and grip; the fourth and fifth fingers could not be fully extended. His speech became nasal and he could not hold up his head easily. A diagnosis of myasthenia gravis was made almost immediately; an injection of neostigmine made him feel "like a new person." In August, 1947, he had a relapse, requiring an increase to 24 tablets a day. On March 1, 1948, under anaesthesia induced by cyclopropane, thymectomy was accomplished through a midline sternal approach; the thymus was removed without difficulty. Involution was slight; germinal centres were seen in large numbers. The patient felt a little worse after the operation and was maintained on neostigmine by injection. He gradually changed to 22-24 tablets a day. Some days he was able to reduce this to 18. There was not much improvement in the first year, but subsequently he gained rapidly, and by August, 1949, his condition was classed as "good to excellent."

Comment on Case 21.—The chief characteristic in this patient was the slow response to thymectomy. Remission was not marked until the second year after operation. The large amount of neostigmine required before operation did not prevent a good result, although the improvement was delayed.

Case 25.—An unmarried graduate nurse was first admitted on May 17, 1948, at the age of 35. She first noted difficulty in speaking and swallowing, and general weakness, while recovering from rheumatic fever in 1942. Six months later a test for myasthenia gravis was made, with dramatic results. She was adjusted on 10 to 14 tablets of neostigmine a day. Two courses of x-ray treatment were followed by a remission, reducing her intake to four or five tablets. A relapse in 1946 necessitated 18 tablets. The patient did well on this schedule until 1947, when another relapse occurred and the dosage was increased to 25 tablets. In March further x-ray treatment of the thymus brought no improvement. She had great difficulty with facial and ocular musculature. On May 21, 1948, under anaesthesia induced by cyclopropane, thymectomy was accomplished through a midline sternal approach; the thymus was removed without difficulty. Involution was marked; no germinal centres were seen.

The patient's post-operative condition was satisfactory; her general strength was good, she was able to smack lips, close eyes fairly tight, and hold out fingers. She relapsed, and neostigmine was gradually increased to 47-48 and finally to 57 tablets, and then was gradually reduced to 42. The patient was stronger, better adjusted, and felt much better than in September, 1947. Six months after operation she had a difficult time, with frequent and severe colds, but finally she was able to return to her regular schedule of 32 tablets a day. Eight months after thymectomy she was still on the same schedule, but symptoms and complaints were less severe than previously. She works in her office from 8.30 a.m. to noon every day.

Comment on Case 25.—Immediately after operation the patient relapsed. Neostigmine dosage had to be raised to 57 tablets a day before good adjustment was accomplished—a larger dose than any previous patient in our series had required. I was not under the impression that the patient was "resistant" to the medication, only that her needs were large because of the depth of her relapse. Adjustment was good at her high level of intake, almost as good as any seen in patients requiring large amounts of neostigmine. She was not improved by additional intramuscular treatment, for this only evoked parasympathetic stimulation without affecting the myasthenia gravis. We have come to disregard the amount of neostigmine needed to carry a patient through a relapse, realizing that, if the patient is to survive, the "deficiency" must be made up no matter what the amount required. *Most instances of "resistance" are examples of underdosage.*

Case 27.—This patient, a single woman, was first admitted on August 10, 1948, at the age of 22. In 1943 she noted progressive difficulty in swallowing and talking. Six months later there was gradual onset of weakness of knees and legs, and ptosis; weakness would begin about one hour after awakening. The patient was able to eat breakfast but not other meals. Neostigmine relieved her symptoms so that she was able to work

as a part-time salesgirl. In 1947 her symptoms returned and her intake was increased to five tablets a day. In April, 1948, she developed weakness of her hands and had to stop work for an hour and rest. On August 16, 1948, under anaesthesia induced by cyclopropane, thymectomy was accomplished through a midline sternal approach. The thymus was removed without difficulty. Involution was slight; germinal centres were found frequently.

After operation the patient was maintained on 10 tablets a day. About a month later she was able to reduce her intake to two tablets, and felt about 85% better than previously. She was able to return to work. In May, 1949, the patient was taking half a pill in the morning and occasionally half a pill at night; there were no symptoms of myasthenia on this dosage.

Comment on Case 27.—The response to thymectomy occurred within a month and has remained nearly complete for the first post-operative year. The result was excellent—as good as in Case 19, but the response in this case was more prompt.

THYMOMA SERIES

Seven patients in the total series of 36 treated by thymectomy proved to have a thymoma embedded in or replacing most of the thymic tissue. Six of the tumours have been described in detail by Castleman and Norris (1949), comprising Nos. 1, 2, 3, 4, 6, and 8 of their series of 10 cases, the other four being necropsy specimens and therefore not included in our thymectomy group. One additional case (No. 28) not reported by Castleman and Norris (1949) has been used in our series.

Of the seven patients with thymoma, only three were living in 1949: one had survived six years (Case 8); one, two years (Case 15); and one, nine months (Case 28). Two of the four non-survivors were "operative deaths," occurring 24 hours (Case 5) and four days (Case 14) after thymectomy; each of the other two patients died of myasthenia gravis one-and-a-half years after operation (Cases 6 and 20). In the course of the years since our first thymectomy for thymoma (Case 5), in July, 1942, much has been learned about the type of patient who can survive such an extensive surgical procedure as thymectomy, the patient's needs for a balanced medication during and immediately after the operation, and the optimal time for doing the operation. The knowledge acquired, which may be modified as more experience is had, is illustrated by the following selected case reports and the comment on them.

Patients with Thymoma Surviving Thymectomy (3 Cases)

Case 15

A married woman was first admitted on October 15, 1946, at the age of 47. One year before admission she first experienced general fatigue and ptosis. Because of serious illness in her family, her condition was thought to be on a psychogenic basis. Three months before admission her condition had progressed; her voice became nasal, food regurgitated through her nose, there was difficulty in chewing, and weakness of arms prevented her from being able to comb her hair. Her symptoms were made worse by activity and relieved by rest. A diagnosis of myasthenia gravis was made and subsequently neostigmine was given by mouth, 15 mg. four times a day. On this medication her symptoms disappeared.

Course of Disease.—Still maintained on four tablets a day, the patient was admitted to the hospital because a radiograph revealed an oval, sharply defined, smoothly rounded mass lying in the left upper mediastinum, anteriorly. The anterior border almost touched the sternum. The mass was lobulated and there was some calcification near its margin. Because of the mediastinal tumour, thymectomy was advised although the short duration of her symptoms, the quick and adequate response to neostigmine, and the mild nature of her disease were not thought to be important enough to justify the operation.

Thymectomy, November 18, 1946.—The patient received 10 mg. of neostigmine methylsulphate and 2 mg. of atropine sulphate in 1,500 ml. of a 5% dextrose solution, given intravenously during a period of about eight hours during and following the operation. Anaesthesia was induced by cyclopropane. Thymectomy was accomplished through a mid-sternal approach, and the thymus and a mass consistent with a thymic tumour were removed without difficulty.

Pathology.—The tumour is described and pictured by Castleman and Norris (1949) as Case 3 in their series. It conformed to pattern II, with about an equal number of epithelial cells and lymphocytes. The uninvolved thymus was greatly involuted, with a few questionable germinal centres present in the medulla.

Post-operative Course.—The patient's condition following the operation was excellent and she was relieved of some symptoms immediately. Five days after operation all medication with neostigmine was discontinued, as she was free of myasthenia symptoms. She has been symptom-free since the operation, a period of two years and nine months. There has been no recurrence of the thymoma in the mediastinum.

Comment on Case 15

The response to neostigmine by mouth was so efficient in this case that without the mass in the mediastinum thymectomy would not have been advised. Our policy has been to control patients by oral medication, without operation, when the adequate maintenance dose is about 12 or fewer tablets a day. As spontaneous remissions in myasthenia gravis are not infrequent, this patient might have responded as well to medication as she did to thymectomy. The disclosure of the mass by radiograph made operation justifiable, although not an emergency. One of our patients, not in this series, has survived since 1935 with a mass in the mediastinum: although an example of severe myasthenia gravis, thymectomy has not been done, partly because of the patient's marked tendency to remissions, both spontaneous and during pregnancy (Viets, Schwab, and Brazier, 1942, Case 7).

The finding by radiograph of a mass in the anterior mediastinum in a myasthenic, however, indicates with a high degree of probability that a thymoma is present. Operation may or may not be advised, the decision being based on the total picture of the patient's illness and not solely on the dramatic disclosures by radiograph. Some thymomas take on an invasive character, although, as Castleman and Norris (1949) state, "By and large, the thymoma of myasthenia gravis should be considered as a benign neoplasm." An example in our series of local spread is detailed below in Case 20. Implantations may occur, but, at least in some cases, these are post-operative, as in our Case 6. Tumours of the size found in this patient, however, may become adherent to the pleura and encompass the phrenic nerve. Removal therefore was indicated on the grounds of obstruction, although the condition in the mediastinum could not be visualized before operation.

The prompt remission after operation, plus the duration of the improvement over a period of two years, was encouraging. Remissions of equal quality, without thymectomy, in early mild cases such as this patient showed are too common to make one feel that the operation resulted unmistakably in her improved state of health. Time only will supply the answer to the question of prognosis. The pathological changes in the thymus fully justified the removal of the tumour in this patient, no matter what effect the thymectomy may have on her myasthenia gravis in the future.

Case 28

A single male mill worker was first admitted on January 31, 1940, at the age of 28. He first developed symptoms in November, 1939, when he awakened one morning with ptosis and diplopia. Within a few weeks difficulty in chewing developed and liquids regurgitated through his nose. When singing in church he noticed a nasal quality to his voice. These symptoms were followed by generalized weakness of arms and legs, and at one time his right leg gave way and he

fell. He was able to raise himself, but fell again and had to be carried indoors. On admission to hospital the diagnostic test was strongly positive (Schwab and Viets, 1938), and a diagnosis of myasthenia gravis was made (Mattis, 1941, photograph).

Course of Disease.—The patient was started on 11 neostigmine tablets a day, but the dosage was soon reduced to six a day. When difficulty in swallowing continued, an extra tablet was required before the morning and noon meals. After three weeks in the hospital he was able to go back to work in the mill, and for the next eight years he was well maintained on three to six tablets a day. His course was slightly irregular. By varying his intake slightly on a few occasions he was at one time able to go a whole year on 100 tablets. He curtailed his social activities only slightly. When he re-entered the hospital in November, 1948, nine years after the onset of symptoms, he still had traces of myasthenia. When medication was omitted there was considerable difficulty in swallowing and talking, although not quite as severe as in 1940. He again responded quickly to the diagnostic test. Radiographs of the chest were negative for thymic tumour.

Thymectomy, November 29, 1948.—The patient was maintained during the operation on eight-hour intravenous medication, containing 1 mg. of neostigmine methylsulphate. Anaesthesia was induced by cyclopropane, gas, and ether. Thymectomy was accomplished through a midline sternal approach; in the centre of the thymus was a non-invasive, definite, rounded hard nodule, which was removed without difficulty.

Pathology.—The nodule proved to be a thymoma conforming to pattern II. The surrounding tissue showed germinal centre formation similar in appearance to the non-neoplastic thymus of myasthenia gravis.

Post-operative Course.—The patient's immediate post-operative condition was excellent. On the sixth post-operative day he was well maintained on two tablets of neostigmine by mouth. His facial expression was as good as when following a diagnostic injection of neostigmine. After leaving hospital he continued to do very well, and after four months required no medication. His singing voice had improved in quality and range, even better than it was in 1939 before the onset of the disease. He was working steadily at a lathe in a mill without signs of fatigue (August, 1949).

Comment on Case 28.—After an explosive onset this case was characterized by a therapeutic remission lasting over eight years. Although well maintained on a moderate dosage of neostigmine during this period, the patient was never entirely free from symptoms. Thymectomy brought a complete remission. The post-operative observation period is short, but the immediate response to operation was unmistakable and more pronounced than had ever occurred under medical treatment. The disclosure of a thymoma at operation was unexpected. In spite of the tumour, the patient's reaction to neostigmine and response to operation were not dissimilar to that observed in non-neoplastic thymus cases.

Case 8

A married foundry worker was admitted on September 9, 1943, at the age of 28. In 1942 he noticed that his arms tired easily. It was difficult for him to bathe and dress at night after work. A week later, weakness of his jaw, with difficulty in chewing, occurred. When first seen, in 1943, his chief symptoms were general weakness, dysphagia and dysarthria, ptosis, mask-like face, and weakness of jaws. A test dose of neostigmine was dramatically effective.

Course of Disease.—He did quite well on a regime of 10 tablets of neostigmine a day and was able to do some light work. Three months before admission (June, 1943) he was doing so well that he decreased his intake, but a month later he had an exacerbation of his symptoms, with additional weakness. In spite of an increase of his dosage to 20 tablets, he did not return to his former status. At this time he had weakness of his legs, and four days before admission he suddenly collapsed while at work.

Thymectomy, September 27, 1943.—During the operation the patient received 16 mg. of neostigmine methylsulphate intravenously in eight hours. Anaesthesia was induced by a gas-oxygen-ether mixture. Thymectomy was accomplished through a midline sternal approach. Attached to the lower left arm of the thymus was an oval mass measuring 3.5 by 2.5 by 1.5 cm.

Pathology.—This case was reported in detail by Castleman and Norris (1949) (Case 1), illustrated with six photographs. The thymoma conformed to patterns I and II. The uninvolved thymus resembled in part the moderately involuted thymus of an adult; Hassall's corpuscles were present, with a rare germinal centre.

Post-operative Course.—After the operation the patient was adjusted on 20 tablets of oral neostigmine a day, about the same dose as he had required before operation. He slowly improved, and five months after operation he was fairly well maintained on his schedule of 14 to 16 tablets a day. He missed his medicine immediately if he did not take it, but he felt he had improved. He maintained this improvement through the subsequent six years, although unable to work. In May, 1947, he re-entered the hospital for *re-exploration of the mediastinum*. No further thymic tissue was found. On discharge he returned to neostigmine tablets, taking 16 a day. When last seen in August, 1949, he was taking 14 tablets a day. His voice was nasal and his swallowing poor.

Comment on Case 8

This case was reported in a previous paper (Viets, 1945, Case 5, two photographs). The results of thymectomy were disappointing—so much so that re-exploration was done in the hope of finding an aberrant thymus, overlooked at the time of the first operation. No neoplastic or other thymic tissue was found. After thymectomy the patient's course became more steady, and in spite of the need for large doses of neostigmine he felt "safe," sure that the neostigmine would not fail him in times of stress or become less effective. This feature of lessening of the depth and height of the relapses and remissions following thymectomy is often a favourable effect of this operation. Nearly all patients are impressed by the post-operative evenness of their course compared with the pre-operative period. Although the operation in this case is a "failure," the patient would consider himself 25 to 50% improved.

Operative Deaths from Thymectomy (2 Cases)

Case 5

An unmarried crane operator was first admitted on July 20, 1942, at the age of 41. In August, 1941, he had regurgitation of liquids through his nose. In a few days he developed ptosis, weakness of the hands, and dysphagia. His symptoms varied with the amount of work he did; they disappeared after rest. About three months after the onset, neostigmine by injection gave him complete relief of all his symptoms in half an hour.

Course of Disease.—He was able to continue his work on four tablets, plus a few injections, but he was not well controlled. His weight dropped from 265 to 222 lb. (120 to 101 kg.). His symptoms were not controlled on 11 tablets, and the dosage was gradually increased to 16 tablets; on admission to hospital he was given 20 tablets a day.

Thymectomy, July 23, 1942.—Neostigmine was given by injection before operation. During the last half of the thymectomy the patient was unable to breathe spontaneously and was maintained by artificial respiration. Anaesthesia was induced by a gas-oxygen-ether mixture. Thymectomy was accomplished through a midline sternal approach. The thymus, which appeared grossly normal, was removed, but the operation was a difficult one, requiring over four hours.

Post-operative Course.—The patient was put into a respirator immediately on his return from the operating-room. He also received neostigmine and atropine. He did not regain consciousness and was very restless, ripping off his bandages. On the first post-operative day he was still not responsive, but seemed to be in relatively good condition, with normal temperature, good colour, and warm skin. He suddenly became cyanotic, and despite the fact that the respirator was

working satisfactorily his air exchange was not adequate. He died on the second post-operative day.

Pathology.—The thymic tissue was moderately involuted. Hassall's corpuscles were present in normal numbers; many germinal centres were seen in the medulla.

At necropsy a thymoma was found at the root of the left lung anterior to the bronchus. The tumour conformed to patterns I and II. Reported by Castleman and Norris (1949, Case 2), with three photographs.

Comment on Case 5

The operation, at the time of a relapse in the disease, was one of desperation. This was one of our early cases (1942), and taught us a lesson: *thymectomy should never be undertaken as an operation of desperation*. Patients in a state of relapse present such a severe surgical risk that operation under these circumstances is not justified. Secondly, without adequate neostigmine maintenance during anaesthesia, operations are often hazardous. Subsequent to our experience with this patient we learned to give neostigmine intravenously, a discovery that removed the danger of sudden myasthenic collapse while the patient was unconscious. No operative deaths have occurred in our entire series since December, 1945 (Case 14), a period covered by 22 consecutive cases. This favourable result can, at least in part, be attributed to the balanced maintenance of the patient by intravenous neostigmine during operation. As the result of the necropsy on this patient we learned that a tumour might not disclose itself at operation. Owing to many disturbing factors, a complete exploration could not be done; the tumour was overlooked and found only at necropsy.

Finally, the post-operative care was inadequate. With intravenous medication, as carried out on later patients, myasthenic crises are avoided and maintenance is so controlled that the chances of recovery from thymectomy are greatly enhanced. Patients are not infrequently out of bed on the second or third day, and even are ready to leave the hospital before stitches are removed on the eighth post-operative day.

Case 14

This patient, a single man, was first admitted on November 21, 1945, at the age of 28. In 1941 a mass at the right border of the heart, thought at first to be a dilated auricle, was disclosed by x-ray examination. At that time he was free of symptoms suggesting myasthenia gravis, but he had noted easy fatigue and occasional dyspnoea for a period of five years. Immediate x-ray treatment is reported to have decreased the size of the mass. When first seen in 1942 he was symptomless except for the changes noted in the radiographs. A satisfactory clinical diagnosis could not be made; the mass suggested lymphoma, dermoid, or aneurysm. In 1943 transient diplopia, with mild dysphagia and dysarthria, all symptoms responding quickly to neostigmine, made a diagnosis of myasthenia gravis tenable. The patient responded quickly to treatment and a good remission, lasting nearly two years, followed.

In 1945, however, he had a severe relapse. By midsummer he was only partially maintained on 16 tablets of neostigmine a day. He lost 35 lb. (16 kg.) in four months and could swallow only with great difficulty. Medication was increased to 22 tablets a day, and operation was undertaken under the unfavourable conditions of an increasing relapse.

Thymectomy, December 8, 1945.—During operation the patient was maintained on intravenous medication of neostigmine at the rate of 1 mg. and 0.15 mg. of atropine an hour, so that in 24 hours he received 24 mg. of neostigmine and 3.6 mg. of atropine. Anaesthesia was induced by cyclopropane. Thymectomy was accomplished through a midline sternal approach; the thymus and tumour mass shown by radiograph were removed without difficulty.

Pathology.—The greater part of the tumour had undergone necrosis, being converted into an amorphous mass. The viable portions conformed to pattern II. The rim showed an occasional Hassall's corpuscle, and a single germinal centre was seen (Castleman and Norris, 1949, Case 8).

Post-operative Course.—After the operation the patient showed weakness and difficulty in respirations. He was given oxygen by nasal catheter and supplementary neostigmine by intramuscular as well as intravenous infusion. On the third post-operative day he was restless and twitching in bed, with an elevated pulse rate. Intravenous medication was discontinued. Next day he suddenly sat up on the edge of the bed, gasping. He soon became pulseless and respirations ceased.

Comment on Case 14

The most unusual feature of this case was the early disclosure of the thymoma by radiograph before unmistakable signs of myasthenia gravis developed. The unexplained fatigue noted by the patient many years before 1941 should have suggested the diagnosis. Moreover, the tumour mass, shown by radiograph, was entirely consistent with a thymoma. *When a mass which is clearly not an aneurysm is seen by radiograph in the anterior mediastinum in a patient whose full and detailed history reveals some symptoms of abnormal fatigue of voluntary muscles, no matter how slight, with recovery on rest, a diagnosis of myasthenia gravis, with thymoma, must be entertained.*

Operation, as in Case 5, was done at a most unfavourable time. Even with attempted intravenous treatment success could not be expected, as we were not sure, before operation, of the patient's full requirement for a balanced regime. The patient's requirements were changing (in this case increasing) and accurate measurement was impossible. Thus the rule of avoiding an operation of desperation was again disregarded in 1945 as it had been in 1942. Patients must be "levelled off" on neostigmine before intravenous needs can be measured, and that was not done in this case, the last in our series that failed to survive operation.

Intravenous Medication

The rule for intravenous medication may be conveniently stated here. As previously stated, each oral tablet of neostigmine bromide (15 mg.) is about equivalent in effectiveness to 0.5 mg. of neostigmine methylsulphate given intravenously. Thus a patient taking 12 tablets by mouth in 24 hours, or four in eight hours, requires 2 mg. of neostigmine methylsulphate intravenously in an equivalent eight hours. This may be conveniently added to 1,500 ml. of dextrose or saline and given intravenously just before, during, and after the operation. If the patient cannot swallow at the end of eight hours a second intravenous drip may be started, with a like amount of medication.

We have sometimes continued such treatment for 24 hours or longer, until such time as the patient could return to oral medication, either by tablet or tablets dissolved in syrup, or when treatment with neostigmine, in the case of a favourable and immediate response, was no longer needed. Patients taking 24 tablets a day require 4 mg. in eight hours, and so on. The dosage should be fixed for a week or more before operation. Watch for remissions and relapses. Only operate when the patient is steady, fully maintained, and well balanced on neostigmine. Hasty operations are sure to be unnecessarily hazardous.

Death from Expanding Tumour

Case 20

This patient, a married woman, was first admitted on December 18, 1947, at the age of 31. She had noted difficulty in swallowing in May, 1944. X-ray examination disclosed a mass in the anterior mediastinum. The shadow is reported to have decreased in size after x-ray treatment. In a few weeks her dysphagia subsided, only to return in about six weeks. In 1946 she developed diplopia and ptosis, dysarthria, marked dysphagia, and general muscle weakness. At that time a diagnostic test for myasthenia gravis was positive.

Course of Disease.—The patient continued to relapse in 1947, but finally a maintenance dose was established at 32 tablets a

day—four tablets every two hours. On this dosage, higher than average, she was free from symptoms. Subsequently she was able to reduce her dosage to 16 tablets, but with the onset of a cold she relapsed and raised her intake to 24. Her condition was never satisfactory, as good balance could not be retained. On awakening in the morning she had to be helped until tablets could be taken; within 20 minutes she could get up, dress, and eat. She entered the hospital in December, 1947, for adjustment of her medication. While in the hospital she stopped taking neostigmine for 11 hours, at the end of which time her face was expressionless, her voice was nasal, and she was hardly able to stand; she also had difficulty in holding up her head, chewing, and swallowing. She responded promptly to a diagnostic test, all symptoms disappearing. Because of the mass in the mediastinum, an exploration of the area appeared to be justified.

Thoracotomy, December 23, 1947.—Anaesthesia was induced by cyclopropane. The tumour was enormous, filling the mediastinum. One portion was dense and adherent to the aorta. Removal was impossible; biopsy specimens were taken.

Pathology.—The firmer portions of the tumour conformed to pattern I, being largely epithelial in character. An occasional mitosis was seen. The softer areas were composed predominantly of lymphocytes conforming to pattern III (Castleman and Norris, 1949, Case 4, with two photographs).

Post-operative Course.—The patient had no untoward symptoms after the operation. Her myasthenia was somewhat better controlled than in the past and she was well maintained on 14 tablets a day. Because of the nature of the tumour disclosed at operation, daily x-ray treatment was given over the anterior mediastinum for about three weeks, using 200 r to 300 r at a time. During the course of the next year she was distinctly improved. At times she was able to reduce her medicine to nine tablets a day. About 18 months after the operation she developed a respiratory crisis, and she died in March, 1949, at the age of 33. Details of the necropsy are not available at the time of writing (August, 1949).

Comment on Case 20

The chief interest in this case lies in the discovery of a thymoma about the time of the onset of the patient's first symptoms. The tumour apparently responded to x-ray treatment in that the size of the shadow was decreased. The patient's symptoms, however, for the subsequent three years were unchanged, and she had the usual remissions and relapses in her symptoms of myasthenia. A sudden relapse three years after the onset led to a definite diagnosis and treatment with neostigmine. The therapeutic response was excellent, apparently as good as that experienced in patients without thymoma. Operation was undertaken at about the time that the patient was having a second relapse, but she was fairly well adjusted on medication and it seemed a favourable time for an exploration of the tumour.

At operation the entire anterior mediastinum was filled with tumour, some of it firmly adherent to the aorta and adjacent tissues; total removal was impossible. Biopsy specimens disclosed a thymoma, largely of the epithelial type. After the operation the patient again responded well to medication, and her course was similar to that seen in many patients without tumour. Details of the myasthenic crisis which occurred at the time of her death are not available, and there is no way of telling how much this was affected by the presence of the tumour. In general, one would feel that the tumour in this case did not change the pattern of the disease, although it may have definitely affected the course and led to the patient's death five years after the disease was first discovered.

Death Subsequent to Thymectomy

Case 6

This patient, a married man, was first admitted on March 17, 1942, at the age of 34. The disease began abruptly with rapid increase in symptoms. Within two weeks he developed weakness of his arms, diplopia, difficulty in chewing, and slight dysphagia. His speech became slurred and there was a tendency

for his jaw to hang half-open in the evening. Just before admission to hospital he fell because of weakness while walking upstairs.

Course of Disease.—His immediate response to neostigmine was excellent. The diagnostic test was strongly positive, including response to the swallowing reflex under fluoroscopic control (Schwab and Viets, 1941). He was adequately maintained on 10 tablets of neostigmine a day, by mouth, and subsequently returned to work for the next year moderately relieved but not entirely free from symptoms. He was unable to continue his occupation as a steel worker, and became a watchman, a position that did not involve the lifting of heavy objects. In about a year's time he had a moderate relapse, with increasing difficulty in chewing and swallowing. An increase of medication to 15 tablets a day only partially compensated for his weakness. He returned to hospital, but a satisfactory maintenance dose of neostigmine was not found. In spite of this, thymectomy was carried out.

Thymectomy, April 21, 1943.—The operation was carried out successfully under subcutaneous injection of neostigmine. Anaesthesia was induced by a gas-oxygen-ether mixture. Thymectomy was accomplished through a midline sternal approach. On opening the thorax, respirations ceased and artificial respiration was maintained from that point on. The thymus contained a tumour and was removed, in spite of its adherence to pericardium, without special difficulty.

Pathology.—The tumour was uniformly constituted and had nearly equal amounts of epithelial and lymphocytic tissue corresponding to pattern II. A few Hassall's corpuscles appeared to have been folded into the tumour along with bits of thymic tissue. No mitoses were found.

Post-operative Course.—The patient's immediate condition after operation was poor. He remained in the respirator for three days. On the eighth post-operative day he showed definite improvement and was able to swallow without difficulty. His neostigmine dosage was reduced to seven to eight tablets a day. In the six months following operation he improved steadily, reducing his intake to as low as two tablets a day. Within three months he returned to work. His position at the time required extensive walking, some of it up and down stairs. He lost weight steadily, and at the end of about a year began to relapse and had increasing difficulty in swallowing and sometimes in breathing. In October, 1944, about two and a half years after the onset of his illness and one and a half years after his thymectomy, he developed an acute respiratory infection. On re-entering the hospital he was cyanotic and in coma. He responded dramatically to 0.5 mg. of neostigmine methylsulphate given intravenously, but the response could not be maintained in spite of continued intravenous treatment and the use of the respirator. The patient died within 24 hours of entering the hospital.

Necropsy.—A small tumour attached to the pleural surface of the left diaphragm, showing the same basic structure as the tumour removed at operation, was discovered. It had infiltrated the diaphragm, and the muscle fibres in groups and individually were separated and surrounded by tumour tissue in which both epithelial and lymphocytic elements were present (Castleman and Norris, 1949, Case 6, two photographs).

Comment on Case 6

This patient presented many problems in regard to treatment. The explosive nature of the onset of symptoms at the age of 34, particularly with dysphagia, dysarthria, and weakness of chewing, made the prognosis grave. In spite of the immediate response to neostigmine taken by mouth, he relapsed within a year. Thymectomy was carried out with the patient only moderately well adjusted to neostigmine treatment and during a definite relapse in his symptoms. Subsequently it was realized that this was an unfavourable time for operation. The patient, moreover, was poorly maintained during the operative period, as the use of neostigmine by the intravenous route had not been discovered.

In spite of this hazard he not only survived the operation with the aid of artificial respiration but actually improved in the following year. His dosage of neostigmine was reduced

from 16 tablets to 4 by the spring of 1944, the operation having occurred in April, 1943. A mistake was then made in allowing him to return to an occupation that was taxing his strength beyond justification. He walked as much as 10 miles a day, some of it up and down stairs. During this regime he steadily lost weight again and symptoms increased. It was necessary for him to raise his neostigmine intake to 15 tablets a day. A respiratory infection occurring at this time soon overwhelmed him, as his resistance, particularly to infections of the respiratory system, was low. However, he responded at this time to intravenous medication, but died of respiratory failure within 24 hours.

The most important finding at necropsy was the presence of a piece of thymic tissue growing as a tumour attached to the diaphragm. It was identical in structure with the thymic tissue removed 18 months before. It seems likely that this diaphragmatic lesion represents an accidental surgical transplant; it was not interpreted as a metastasis, as the primary tumour was not malignant. There were no other metastases. The diaphragmatic tumour was not destructively invasive. The opening of the left pleural sac allowed a fragment of mediastinal tumour to be introduced into the pleura and settle in a more dependent place, and this ectopic lesion caused the growth of large numbers of newer-formed capillaries similar to those seen in response to a mild chronic irritant (Castleman and Norris, 1949, p. 51).

General Summary

Of the 36 patients subjected to thymectomy at the Massachusetts General Hospital since 1941, seven had thymomas and 29 showed various degrees of involution and the formation of germinal centres in the thymic tissue.

Three of the seven thymoma patients are living; one has survived six years. Two are greatly improved by the operation and their condition is classed as "excellent"; one is considered "fair."

All but four of the 29 patients in the non-neoplastic series have survived. Their results are classified as "excellent" (3); "good to excellent" (2); "good" (5); "fair to good" (2); "fair" (2); "poor to fair" (2); "poor" (2); "too soon to estimate" (7).

Thymectomy should never be an operation of "desperation." Patients should be adequately maintained on oral neostigmine before operation and their course should be steady.

Neostigmine may be given with advantage intravenously during thymectomy. Approximately 0.5 mg. of neostigmine methylsulphate, given intravenously, is equivalent in effect to 15 mg. of neostigmine bromide by mouth.

Thymomas in general are benign tumours, but they may expand locally. Implants at the time of operation are possible.

The significance of germinal centre formation in the thymus is not clear. The finding of a large number of germinal centres, however, is highly suggestive of myasthenia gravis.

The results of thymectomy in the last nine years justify the continuation of the operation in patients with myasthenia gravis. The operative mortality should be zero, or close to it, if patients are carefully selected and adequately maintained during the procedure.

ADDENDUM

Since this paper was prepared, the report by Keynes (1949) on his large experience with thymectomy in myasthenia gravis has been published. Although he has approached the subject from a slightly different direction, our essential conclusions are identical. Both papers point out the value of thymectomy as a form of treatment for the disease. He, operating on a considerable number of patients, regardless of duration of symptoms or the length of treatment with neostigmine, has provoked a significant remission in 65% of the cases so treated. In his experience, the shorter the history the better the results. I have chosen the more conservative approach, selecting, in most instances, patients long accustomed to the disease and the effects of neostigmine, as a fitting basis for evaluation of an operation radical in type and offering considerable hazard. Keynes has done much to lower the formerly high operative mortality, and it should now be well below 5%.

Only in details do we diverge. My older cases, contrary to Keynes's general assessment, have done fully as well as the cases of brief duration. I have deliberately avoided operating upon mild cases, or those fully maintained under oral medication. Good remissions may often be provoked by judicious treatment with neostigmine alone. Some, in my hands, are complete and of long duration; indeed, equal to those seen after thymectomy. I would consider less than half of 300 patients seen since 1935 as proper candidates for thymectomy, based on our present knowledge of the variable course of the disease. Patients with few symptoms, those responding in a balanced manner to neostigmine, no matter what the dose, most patients over 40 years of age, and particularly those having wide swings of remission and relapse, are not, as I view the problem to-day, best treated by thymectomy.

Secondly, I have not seen "myasthenic crises" characterized by excessive bronchial secretion. Patients may drown in their own secretions, but this, in my experience, is due to excessive or ill-considered use of neostigmine, not to the myasthenia gravis. Before the era of neostigmine, patients died a "dry death," except for pharyngeal accumulation due to dysphagia and inability to cough. Controlled neostigmine, intravenously, has largely removed this hazard during operation.

Finally, my patients do not "hold on" to neostigmine when the need for it is not present. The drug, a powerful stimulant of the parasympathetic system, is poorly tolerated by the non-myasthenic or the myasthenic in full remission. Tolerance to neostigmine, moreover, does not develop. Patients who have been taking the drug since 1935 still find it as effective to-day as when the first tablet or injection was given. That is why it is so valuable over the "long pull"; few other forms of medication can equal it in this respect.

Keynes's experience with 155 patients and his careful analysis of his results have set a pattern traditionally expected of British surgery. Others can only follow and report their results until such a time as general conclusions are justified. That time has not yet come. The key has been fitted to the lock and even partially turned, but the door is not open and what lies behind has not been even disclosed.

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An article in the *Ministry of Labour Gazette* (December 29, 1949) describes the Ministry's efforts to recruit more nurses and midwives. The situation is said to be improving steadily, though there is still urgent need for more recruits to these professions. During the twelve months ended September 30, 1949, 42,000 interviews were given and 15,000 vacancies were filled. Of these, 3,000 were for trained nurses and midwives, 6,300 were for students, and 6,100 were for unqualified nursing staff. Since the war there has been a general improvement in the staffing of hospitals and the health services. During the year ended June 30, 1949, the number of nursing and midwifery staff employed in hospitals rose by about 15,000, and the number of occupied beds rose by 10,000. The number of students training to be nurses has greatly increased in recent years. In 1943 there were about 43,300 students training to be nurses or midwives; in 1949 the number was 57,800. The demand for nurses continues to increase, and there are still no fewer than 30,000 vacancies on the books of the nursing appointments offices.

PROGUANIL-RESISTANT FALCIPARUM MALARIA IN MALAYA

BY

J. F. B. EDESON, M.B., Ch.B.

AND

J. W. FIELD, M.D.

From the Institute for Medical Research, Federation of Malaya

Some of the earliest and still the most complete trials of proguanil ("paludrine") in falciparum malaria were made in 1946 by the Australian Medical Research Team directed by Fairley in Queensland (Fairley *et al.*, 1946). The results seemed decisive: strains of *Plasmodium falciparum* of South-West Pacific origin were sensitive to proguanil at important strategic points in their life history. The pre-erythrocytic forms were destroyed by a single minute dose appropriately timed to the infecting bites; and persons bitten many times were fully protected by 100 mg. given every day. The asexual blood forms were equally sensitive: acute infections were relieved by a single dose of 100 mg. and cured by a 10-day course of 300 mg. a day. Exposure of the gametocytes to therapeutic doses of proguanil arrested sporogony in the mosquito.

The wide range, the high potency, and the low toxicity of proguanil in falciparum malaria excited much interest, and as supplies became available clinical trials began in other parts of the world. The results in South-East Asia were generally good: the clinical response in acute attacks of malaria was perhaps slower than with quinine or mepacrine, but the suppressive activity of a weekly dose of 300 mg. or even 100 mg. was high. Elsewhere the results were equivocal—particularly in Africa and Southern Europe, where the tendency to a slow clinical response and the failure to cure seemed to demand reinforcement with a more active schizonticide, and where a daily dosage of 100 mg. was needed for efficient suppression (Bettini, 1948; Walls, 1948; Abbott, 1949; Covell *et al.*, 1949). Geographical strains, it seemed, showed differences in the proguanil sensitivity of the asexual blood forms.

Experimental evidence had shown in the meantime that proguanil sensitivity in malaria is not constant for a given species or strain, but tends to wane with prolonged exposure to the drug. Resistance could be produced experimentally in *P. gallinaceum*, a malaria parasite which infects the domestic chicken, *P. lophurae*, a parasite of ducks, and *P. cynomolgi* in monkeys; a resistance so marked in *P. gallinaceum* that the parasites became less sensitive to the proguanil than were the chicks themselves, and so persistent that it survived passage through the mosquito (Bishop and Birkett, 1947, 1948; Williamson *et al.*, 1947; Rollo *et al.*, 1948; Hawking and Perry, 1948). Still more significant was the experimental production of proguanil resistance in *P. falciparum* and *P. vivax* (Adams and Seaton, 1949; Seaton and Adams, 1949).

Proguanil Resistance in Naturally Acquired Falciparum Infections of Malayan Origin

Experimental trials of proguanil, sponsored by the Colonial Medical Research Committee, began in this institute early in 1947. They were planned to give information on the therapeutic and suppressive activity of the drug in acute malarial infection. The therapeutic tests were made on subjects with naturally acquired malaria admitted from neighbouring rubber estates and kampongs to the Tampin Malaria Branch of the institute.