that from 40 to 80 per cent. fail to take advantage of the supervisory control thus offered to them.

It is apparent that, despite the many and various procedures in use, we are still far from possessing the ideal contraceptive. By reason of the purpose it is intended to subserve and the varying conditions that govern its use, a contraceptive should be cheap, safe, efficient, and simple in application. It is in the interest of the public that the procedure should be under the guidance of the medical profession, but we cannot expect that contraception will become generally available and acceptable until some method is discovered that is freed from the restraints implied in the need for constant medical supervision that are inherent in the best of our existing practices.

Sterilization

In conclusion, some mention must be made of the limitations that surround the use of contraception in preventive medicine. I have referred on a previous page to birth control as prescribed for women who suffer from disease of the kidneys, heart, lungs, etc., and whose health is liable to be endangered by child-bearing or child-birth. In some such cases contraception is of value when

it is carried out with strict attention to the necessary safeguards. At the same time, where the medical state is so grave as to demand complete protection against the risks incidental to child-bearing, contraception may not be capable of providing the absolute assurance that is required. As has been previously noted, even with constant medical supervision contraception is attended with a risk of failure that varies from 5 to 10 per cent. In such cases the security required by the urgency of the medical indications is only to be obtained by sterilization or by the application to the ovaries of sterilizing doses of x rays.

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TREATMENT OF MYASTHENIA GRAVIS

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The treatment of myasthenia gravis was for a long time on an unsatisfactory empirical basis. The reasons for this were twofold. In the first place the natural remissions of the disease were too readily ascribed to the results of beneficial therapy; while, secondly, the nature of the pathological upset was unknown and variously considered to be of neural, muscular, or humoral origin. The first real advance arising out of empirical methods was made by Edgeworth,^{1,2} who in 1930 reported on the effects of ephedrine.³ She was herself a sufferer from myasthenia gravis, and she noticed a steady improvement over three years. Glycine and ephedrine in combination were tried by Boothby³ in 1934, and he concluded that with this treatment "most patients improved sufficiently to permit them to return to work."

The resemblance of the abnormal muscular fatigability in myasthenia gravis to curare poisoning had suggested the myoneural junction as the seat of the pathological process, and Walker⁴ in 1934 drew attention to the effect of physostigmine salicylate, given by hypodermic injection, in remedying this fatigue. The toxic effect of physostigmine prohibited large dosage, but the use of prostigmin, a less toxic analogue of physostigmine, was attended by dramatic results. This work has been confirmed by Pritchard,⁵ Laurent,⁶ and others, and attention has been focused on the myoneural junction.

Dale and Feldberg⁷ have shown that normal transmission of excitation from motor nerve endings to the voluntary muscle fibres is concerned with the liberation of acetylcholine. In myasthenia gravis there may be insufficient liberation, or increased destruction by choline esterase, or the threshold value may be altered by other factors, as Briscoe⁸ suggests. Feldberg and Vartiainen,⁹ working on the superior cervical ganglion of the cat, found that eserine (physostigmine) strongly sensitizes the ganglion cells to injections of acetylcholine, and that potassium ions had a similar but much smaller effect. Eserine

was from sixteen to forty times more powerful than potassium in this respect. These considerations indicated the probable mode of action of physostigmine and prostigmin in myasthenia, and also led Laurent and Walther¹⁰ to investigate the action of potassium chloride given by mouth. They found a demonstrable improvement with large doses of potassium chloride and a useful adjuvant action to prostigmin in small repeated doses.

The following cases of myasthenia gravis were investigated as to the effects of prostigmin, potassium chloride, and physostigmine on their condition.

Clinical Cases

CASE I

A married woman aged 32 was admitted to hospital on July 8th, 1935, complaining of difficulty in speaking and swallowing and that her eyes crossed. The family history was negative, and the previous history was uneventful, except for dysmenorrhoea. For many years she had suffered from attacks of trembling, which came on every few weeks and during which her "inside" and hands used to shake. These attacks were also accompanied by sweating, usually occurred when she was worried, and lasted some hours. Two years ago she noticed that the right eye "would become crossed," and she saw double on looking to the right. She obtained spectacles from an optician, and these seemed to help her until four to six months ago, when the left lid began to droop, and she had her glasses changed, but without any effect on either eye.

During the past few months she noticed an irritation in the throat, which made her cough. For about six weeks she had had difficulty in swallowing, and this had gradually increased. It was not accompanied by any pain, and the difficulty was associated with solids rather than with liquids. At times the food had regurgitated through her nose. Her voice had recently altered and had become quiet, and since she had had the difficulty in swallowing she noticed she was slightly deaf, more so on the left side. For some time the patient had found that she tired very readily, and was unable to carry a shopping bag or walk as far as formerly, and that, whilst eating, her "mouth became tired" and food regurgitated through her nose. After resting, however, the feeling of fatigue passed off, and she was able to resume what she had been doing for a short period before tiring began.

CLINICAL EXAMINATION

On admission the patient was thin, pale, and rather depressed. There was a well-marked left-sided ptosis,

and on the right side the upper lid was retracted. Coarse nystagmus to the right was found, and there appeared to be weakness of the right lateral rectus and left medial rectus. Diplopia was present on looking to the right. The pupils were slightly irregular and reacted sluggishly to light. Both sides of the face were rather weak and the palate moved sluggishly. Dysphagia was observed, and the speech was nasal and slurred. Sensation was not impaired. The thyroid was rather full. The heart, lungs, and alimentary system were normal. X-ray of the skull was negative, and x-ray of the chest for enlargement of the thymus showed a possible slight enlargement. The blood Wassermann and an examination of the cerebro-spinal fluid proved negative, and the impedance angle was normal. The deafness was found to be middle-ear in type and of long duration. After admission the variability of the symptoms was noticed. In the morning they were less marked; thus the ptosis, although present, was slight, while the voice was fairly strong; after conversing for a short time, however, it became nasal in type, and finally faded to a whisper, to recover again after a period of rest. The effects of effort were noticed on the ptosis and palate also.

CASE II

A married woman aged 33 was admitted to the Maudsley Hospital on June 25th, 1932, complaining of depression. In the family history one paternal uncle died in a mental hospital and the father and one brother died of phthisis. The patient had always been nervous and of an excitable disposition, and had had attacks of depression at her periods, which did not begin until she was 19 years old. The main points in the medical history were as follows. She had had an appendicular abscess and tuberculous glands in the neck in 1922, three mastoid operations, in 1923, 1927, and 1929 respectively, the last one being complicated by cervical adenitis, and in addition she had had frequent attacks of quinsy. For about two months before admission she had been losing weight, sweating, sleeping badly, and suffering from headaches and nervousness. She was admitted to a general hospital on January 15th, 1932, when she had tachycardia, tremor of the hands, bilateral exophthalmos, and profuse perspiration. The blood pressure was 168/100, and the basal metabolic rate was +50 per cent. On January 25th she complained of severe abdominal pain, which recurred frequently. This was thought to be due to an acute salpingitis which had spread to the peritoneum. On March 20th she developed signs of a chronic intestinal obstruction, but was considered unfit for operation. The condition was thought to be gonococcal or tuberculous, but smears from the cervix and the complement-fixation test for gonococci were negative, whilst the Mantoux reaction was only positive to dilutions of 1 in 1,000.

MYASTHENIC SYMPTOMS

When the patient wakened on the morning of January 31st, 1932, the right eyelid was drooping, and on February 3rd the ptosis was more marked, the mouth was slightly asymmetrical on talking, and there was difficulty in protruding the tongue. Electrical reactions in the left arm and leg were normal. On February 17th, in addition to the above signs, she complained of diplopia. X-ray of the chest showed no enlargement of the thymus gland. She showed little change until June 8th, when she became depressed, restless, and suicidal, and she was transferred to the Maudsley Hospital on June 25th.

On admission here she was restless, agitated, and depressed, but in addition showed many hysterical features. She was querulous, self-centred, and continually making impossible demands. Physically, in addition to the signs of hyperthyroidism already noted, she showed weakness of the right eyelid and face, left internal strabismus, and at times dysphagia was present. The patient stated she could eat breakfast more easily than her other meals, and her voice was noticed to be hoarse at the end of a conversation. Shortly after admission she developed signs of acute intestinal obstruction, and was operated on on August 5th, when some adhesions were divided. She again became emotional and depressed, and discharged herself against advice on August 20th, 1932.

A thyroidectomy was performed in March, 1933, and after this she apparently remained well until April, 1935, when she became rather depressed and sleepless. She complained of tiring easily, of choking attacks when eating, and of drooping of both eyelids. She also stated that the muscles of her neck went stiff on yawning. She was readmitted to hospital on August 20th, 1935.

On admission she stated she felt at her best at about 10 a.m. and got worse as the day went on. Right-sided ptosis was present, and there was weakness of the right lateral rectus, of both sides of the face (especially the lower part), and at times fluids regurgitated through the nose and she had some difficulty in speaking. The impedance angle was normal.

Mentally she was self-centred, anticipated special attention, and often lay in bed indifferent to anything except her own needs. At times she had retention of urine, showed intractable insomnia, and complained of vague somatic pains.

Method of Investigation

With the smaller doses of the standard solution of prostigmin*—namely, up to 2 c.cm.—reliance was placed on the usual clinical methods, such as counting up to fifty, observing the position of the upper lid, and the dynamometer readings. Effort was assessed by the number of lead shot raised by the upper lid, and also by the excursion of the needle of a sphygmomanometer dial on blowing into it. The last method suggested a means of more accurately recording effort and rate of fatigue. The patient was asked to blow into a rubber tube connected with one arm of a U tube containing mercury, the other arm of which carried a float which recorded on a smoked drum. The patient was asked to blow as forcefully and as long as possible, and a selected number of blowing efforts were recorded at each experiment. It was found convenient to record two consecutive blowing efforts on a fast drum followed by ten on a slow drum, and finally one or two on a fast drum, depending on the degree of fatigue present. Approximately five-second intervals were allowed between each blowing effort.

The amplitude of the excursion of the float recorded half the total column in millimetres of mercury supported by the effort; the measurement is thus a direct one. The photographs are of the original records reduced to one-third, and read from left to right. One patient, Case I, with marked palatal weakness, was asked to pinch her nose firmly during the experiment.

A number of normal controls by this method showed almost no variation in the height and shape of the curve after fifteen blowing efforts, and at different times showed very similar curves. It was therefore assumed that the change in type of curves of these patients was, during an experimental day, due to muscular weakness and fatigue associated with the myasthenic condition and the specific drugs used in its treatment. The blowing effort was thought to be a satisfactory test, considering the wide musculature used and the number of muscles particularly involved in myasthenia gravis. The results were confirmed in one or two experiments by recording on a drum the effects of fatigue on a finger working against a spring. The first series of experiments were done with prostigmin alone.

Results of Prostigmin Treatment

In assessing results three factors were taken into account: the length of time of effect, the time of maximum effect, and the maintenance of the shape of the curve as recorded. With smaller doses—namely, up to 2 c.cm.—objectively, improvement was noted up to about five hours, the maximum effect being reached at about one and a half hours after administration. With the larger doses the effect lasted up to about eight hours,

* 1 c.cm. = 0.5 mg. of prostigmin.

the peak of improvement being noticed about one and a half to two hours after administration. Fig. 1 illustrates these objective findings.

The shape of the curve was better maintained the higher the dosage, the records being considered at comparable times. Subjectively the effect was more prolonged, patients stating that they felt better for much longer periods of time although clinically the signs of myasthenia were again quite marked.

During the course of the experiments toxic symptoms were noted. With 1 c.cm. some discomfort was felt in the abdomen by both patients. With 2 c.cm., fifteen

minutes after the injection Case II complained of shivering, while goose-flesh and pallor were noticed. This lasted for at least thirty minutes, and the abdominal discomfort increased so that she was unable to take a meal. Case I, fifteen minutes after an injection of 2 c.cm., complained of abdominal discomfort and diplopia on looking to the right. Vertical nystagmus was noted. Thirty minutes afterwards diplopia and nystagmus were still present, and five hours afterwards food gave rise to a griping pain.

These toxic symptoms were noticed in increasing severity with the higher doses; both patients complained of definite discomfort, and had to lie down for periods of one hour and longer following injection; atropine, 1/100 grain, was given with doses of prostigmin exceeding 2 c.cm. With 5 c.cm. Case II developed muscular twitchings, and Case I showed definite Rombergism in the first half-hour after injection. Dizziness and photophobia were distressing symptoms, while the pupils were constricted and the pulse slowed.

Potassium Chloride

Potassium chloride was administered by mouth, at first in a single dose of 5 grams, then in a single dose of 10 grams, and lastly in split doses of 3 grams at two-hourly intervals for four doses. With the smaller single dose Case I showed slight improvement, but Case II showed no improvement, the curves becoming progressively worse than before administration. Toxic symptoms were very apparent, and consisted of severe abdominal pains, pallor, nausea, giddiness, and rapid pulse.

With the larger single dose definite improvement was noticed in the curves up to four hours after administra-

tion in both cases (see Fig. 2), but the toxic symptoms were similar to those noticed with the smaller dose, except that they were more severe, and in addition Case I showed double internal strabismus as with prostigmin. With the repeated small doses the curves showed no improvement (see Fig. 3), while the toxic symptoms were again marked and diuresis was particularly distressing.

Prostigmin and Potassium Chloride

An attempt was made to test the prolongation of

the effects of prostigmin by administering potassium chloride at the same time by mouth. The patients were given 5 c.cm. of prostigmin together with 1/100 grain atropine, and two and a half hours afterwards 3 grams of potassium chloride were given and repeated at two-hourly intervals for four doses. The curves showed possibly slight maintenance of effect for between nine and ten hours (see Fig. 4), but the toxic symptoms now almost dominated the picture. Both patients complained of severe abdominal pain, nausea, sickness, and frequency of micturition. Within the period of investigation—eleven hours—urine was voided eight or nine times. Case II jumped "as in a stroke," and felt "dreadful, as if she were going to die," while Case I complained of bearing-down pains.

Physostigmine

Physostigmine salicylate, 1/10 grain, was given by hypodermic injection, and at the same time tinct. belladonnae, 10 minims, was given by mouth

three times a day. The curves showed improvement corresponding to about 4 c.cm. prostigmin, but toxic symptoms were marked (see Fig. 5). Both patients complained of feeling ill and shaky and had to lie down, and Case II nearly choked while drinking her tea. Physostigmine was also given by mouth, with some slight improvement but considerable toxic effect in both cases.

In order to eliminate the possible suggestive effect, if any, on the curves during the period of investigation of prostigmin, injections of 3 c.cm. of sterile water were given. Subjectively the patients stated they felt much better, although the curves showed no improvement (see Fig. 6). No toxic effects were apparent or were complained of.

FIG. 1.—Case I. Records of blowing efforts before and after 5 c.cm. prostigmin. (a) Before injection; (b) 1 hour 40 minutes after injection; (c) 4 hours after injection; (d) 5½ hours after injection. In (b) the maximum effect of the prostigmin is seen.

FIG. 2.—Case II. Records of blowing efforts before and after 10 grams of potassium chloride. (a) Before potassium chloride; (b) 1½ hours after; (c) 4½ hours after.

FIG. 3.—Case II. Records of blowing efforts before and during administration of 3 grams potassium chloride two-hourly for four doses. (a) Before potassium chloride; (b) after two doses; (c) after three doses; (d) 1 hour after four doses.

Commentary

By the use of this method a clinical assessment was attempted of the value of prostigmin in the treatment of myasthenia gravis and the possible adjuvant effect of potassium chloride. With prostigmin alone the increase of muscle power was that observed by others, and can only be called dramatic, but in our experience toxic effects were much more prominent than would have been expected from reading the previous literature. Carmichael¹¹ and others, in a report to the Therapeutic Trials Committee of the Medical Research Council, indicate the effect of prostigmin in reducing the pulse rate and blood pressure. They noted slight sweating and twitching of the muscles, but without discomfort. Aeschlimann and Reinert¹² report no adverse influence on heart rate and blood pressure and little miotic effect in therapeutic doses. Pritchard⁸ comments on the "feeling of stickiness around the orbits" and slight photophobia, with an increased flow of tears. Laurent⁹ noted mild alimentary and ocular symptoms lasting for a few minutes only.

The toxic symptoms in our cases were alimentary, cardiovascular, and nervous, and, caused the complete prostration of the patients up to periods of one hour and longer. A particularly distressing symptom was depression, with intense anxiety and fear of death. It should be stressed that this state of depression was not due to the psychopathic disposition of the patients, as Case I was a most stolid, placid type, although Case II showed many hysterical features.

Potassium chloride given to prolong the effect of prostigmin appeared to be of some slight effect, the positive value of which was counteracted by the notable increase in toxic symptoms and the onset of diuresis. Physostigmine appeared to have effects analogous to prostigmin when given by injection, but toxic symptoms were more marked.

In view of these conclusions it was felt a hopeless proposition to undertake continuous treatment with prostigmin, more particularly when patients were discharged from hospital and were not under constant medical supervision. One patient, Case I, was allowed out on a weekend pass while under treatment, and spent a large part of the time sitting in a chair owing to the toxic symptoms.

The results of prostigmin are indeed remarkable, and must be of great value in critical cases of myasthenia gravis with grave difficulty in swallowing or breathing, but in the less severe cases it would appear to us at the moment unwarrantable to hold out to patients the prospect of returning to a normal mode of life. Indeed, from the psychological point of view the presence of toxic symptoms and the relatively rapid fluctuations between the state induced by prostigmin and the myasthenic state produced periods of severe depression. For these

reasons these patients were discharged and treated as out-patients with glycine and ephedrine, according to Boothby's method. Since the time of their discharge, about four months ago, they have been taking glycine 10 grams three times a day and ephedrine 3/8 grain twice daily. On this they have shown continuous slow improvement.

Conclusions

1. The specific effect of prostigmin in the treatment of myasthenia gravis is confirmed, but its value is considerably diminished by the toxic symptoms and the difficulties in its use outside hospital.

2. Potassium chloride appeared to have little adjuvant effect, but considerably increased the toxic symptoms.

3. Physostigmine in adequate dosage produced apparent improvement, but with greater toxic effects.

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FIG. 4.—Case I. Records of blowing efforts before and during administration of 5 c.cm. prostigmin and 3 grams of potassium chloride two-hourly for four doses. (a) Before prostigmin; (b) 2½ hours after prostigmin; (c) 4½ hours after prostigmin and after two doses of potassium chloride; (d) 7 hours after prostigmin and after three doses of potassium chloride; (e) 9 hours after prostigmin and after four doses of potassium chloride.

FIG. 5.—Case I. Records of blowing efforts before and after 1/10 grain physostigmine salicylate by injection and tinct. belladonnae by mouth. (a) Before injection; (b) 15 minutes after injection; (c) 2 hours after injection; (d) 5 hours after injection.

FIG. 6.—Case II. Records of blowing efforts before and after injection of sterile water. (a) Before sterile water; (b) 1½ hours after injection of 3 c.cm. sterile water; (c) 2½ hours after injection of 3 c.cm. sterile water.