

*Chronic Epidemic Encephalitis.** By P. K. McCOWAN, M.D.Edin.,
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A GREAT amount of work has now been carried out in regard to epidemic encephalitis, which has led to a better understanding, not only of this disease, but of mental disorders generally. It is hoped that our investigations at this hospital can be regarded as a small contribution towards this more complete understanding.

The symptoms now shown by some of our patients appeared first during an attack of acute epidemic encephalitis, and persisted after the disappearance of their other symptoms, but, in the majority, it has not been until a considerable time after their acute attack (this, indeed, often having passed undiagnosed) that the chronic nature of the disease has revealed itself. It is thus seen that a prognosis of the ultimate outcome of an acute attack, no matter how mild, is impossible, and, on the other hand, a definite history of an acute attack is no more necessary to establish a diagnosis of the chronic condition than is a history of syphilis for a diagnosis of general paresis. It is impossible at present to say what proportion of surviving cases of epidemic encephalitis develop chronic symptoms, whether mental or physical. It is especially in children that later mental symptoms are common.

This paper is based on clinical and laboratory work carried out at this hospital and at the Maudsley Hospital. Being convinced from clinical experience, that hyoscine is of the nature of a specific in the treatment of encephalitic Parkinsonism, we considered an interesting line of research would be to find objective proof of its action on the bodily mechanisms in such cases. We first chose carbohydrate metabolism as represented by the blood-sugar curve, and followed this up with intelligence tests, experiments on cerebation and muscular tonus, and investigations into the altered affectivity as shown by the psycho-galvanic reflex. We found objective proof that all these phenomena are abnormal in these patients, and further, that hyoscine made them all approximate the normal. The present paper is concerned chiefly with carbohydrate metabolism as represented by the blood-sugar curve, and to show how this is influenced by hyoscine.

CLINICAL EFFECTS FOLLOWING THE INJECTION OF HYOSCINE.

In the Normal Person.

The subcutaneous injection of $\frac{1}{100}$ gr. of hyoscine hydrobromide is followed in from ten to fifteen minutes by dryness of the

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mouth and throat, giddiness and a slight degree of mental confusion, some inco-ordination shown in slight slurring of the speech and inability to walk straight, and marked impairment of accommodation, with consequent difficulty in reading any but the largest print. These unpleasant early phenomena are followed by a feeling of laziness or fatigue; a great effort is required to perform the simplest movements, and, if left to himself, the individual will settle down in a chair and soon fall asleep, remaining in this state for three to six hours. Thus, the immediate and remote effects of hyoscine in the normal person are definitely depressant in character, and hence differ from those produced in a person suffering from encephalitic Parkinsonism.

In Encephalitic Parkinsonians.

The *immediate* effects of hyoscine are indistinguishable from those met with in the normal person—namely, dryness of the mouth, interference with accommodation, inco-ordination, etc. The *later* or *remote* effects, however, present a marked divergence from those found in the normal individual. A short period of drowsiness lasting for about two hours is often noticed, and is followed by signs of physical and mental improvement. In some cases these beneficial results are more marked than in others, but in practically every case, given the correct dose, some improvement is obtained. On the physical side there is diminution of the generalized muscular rigidity, lessening of the tremors of the face and extremities, and disappearance of the excessive salivation and lacrymation which are such frequent and distressing features of this condition. The patient becomes more alert, and instead of being content to sit huddled up in a chair, he will occupy himself with light tasks, his gait is much freer, his shuffling less pronounced, some expression creeps into his mask-like countenance, and he begins to exhibit interest in things outside himself. His articulation, though lacking in timbre, is less slurring and hesitant, he speaks more freely, and his speech, like all his actions, shows less of the retardation which is such a prominent feature of the disease. If the action of hyoscine is on the motor side of the neuro-muscular arc, it follows that in this action must lie the explanation of the increased sense of well-being, the diminution of the apathy, and the brighter outlook of those who benefit by its administration. It supports the thesis that, though the brain is the seat of the psyche, the functions of the mind are dependent upon the whole body and the harmonious interaction of all its parts, as implied in the time-worn dictum, "*Mens sana in corpore sano.*"

In this connection the effect of hyoscine on muscle tonus is of

interest, but since this work will shortly form the subject of a separate paper no details need be given here.

In the encephalitic it is always difficult to discount the element of suggestion in the appraisal of the benefits derived from any particular form of treatment, but extended experience of the administration of hyoscine in this disease leaves no doubt that in many cases it is, quite apart from suggestion, of profound benefit. The following two cases illustrate this :

CASE 1.—A girl, æt. 17, who suffered from Parkinsonism with excessive salivation, marked general rigidity, and who was completely dependent, requiring hand-feeding, washing, etc., immediately improved on hyoscine hydrobromide $\frac{1}{100}$ gr. daily, and, after three days, was up and about, able to dress and feed herself, was alert and cheerful, and by the end of a week took part in the social life of the ward, including dancing.

CASE 2.—A man, æt. 50, suffering from well-marked Parkinsonism, with rigidity and mask-like features, excessive salivation, entirely dependent and depressed, on hyoscine hydrobromide $\frac{1}{2}$ gr. daily became quite active and cheerful, his rigidity diminished and salivation and tremors disappeared. In order to eliminate the element of suggestion, sterile water was repeatedly substituted for the hyoscine without response.

As regards the suggestibility of the chronic encephalitic, it is more than coincidence that the functional aura is found here to an extent not approached in any other group of patients found in a mental hospital. It appears to us that the site of the lesion in these cases may be all-important, and a clue to the discovery of an organic basis for the so-called functional nervous disorders or psychoneuroses. We are not suggesting that these diseases are not psychogenetic in origin, but that they are not essentially functional in nature, in the sense that organic changes are set up secondary to the functional disturbances, but that these organic changes are the most important element in the establishment and continuance of the disease. No gross material change is suggested, but subtle biochemical or biophysical abnormalities may well be present. The site referred to is the basal ganglia. Certain it is that this area which is affected in encephalitis lethargica, with its hysterical aura, is of prime importance in the instinctive and emotional life of man, and this of course it is which is at fault in the neuroses. Support is lent to this hypothesis by the fact that in chorea and Wilson's disease we have two other diseases which, like encephalitis lethargica, have lesions of the basal ganglia and psychic manifestations of a functional or hysterical nature.

EFFECT OF HYOSCINE ON THE BLOOD-SUGAR CURVE.

We would now like to deal shortly with the laboratory part of these investigations, which was done in conjunction with Capt. Mann at the Maudsley Hospital, and firstly we would say a few

words about the method employed. In order to discover the effect of the injection of $\frac{1}{100}$ gr. of hyoscine hydrobromide on the blood-sugar curve, both in the normal person and in the encephalitic, the following precautions were taken: The person whose blood-sugar curve was about to be investigated was starved for 13 hours (from 8 p.m. till about 9 a.m.). He was kept in bed or seated comfortably in a chair, and the temperature of the room was maintained at about 65° F. A specimen of blood was taken to ascertain the fasting blood-sugar level, and then 50 grm. of glucose in 6 oz. of water were given by the mouth, and at the same time $\frac{1}{100}$ gr. of hyoscine hydrobromide was injected subcutaneously into the arm. Thereafter, specimens of blood were taken at fixed intervals— $\frac{3}{4}$ hour, $1\frac{1}{4}$ hours, $1\frac{3}{4}$ hours, $2\frac{1}{2}$ hours. In encephalitic patients it was necessary first of all to establish blood-sugar curves by giving glucose only, the effect of hyoscine being investigated the following morning.

Effect of Hyoscine on the Blood-Sugar Curve of the Normal Person.

To establish the effect of hyoscine on the blood-sugar curve of the normal person, eight nurses and three medical colleagues were selected, and they were all in good health. In Table I are shown the blood-sugar readings of these at the fixed intervals of time.

TABLE I.

| No. | Sex. | Fasting level. | 50 grm. glucose + $\frac{1}{100}$ gr. hyoscine. | | | |
|-----|------|----------------|---|----------------|-----------------|-----------------|
| | | | After 45 mins. | After 75 mins. | After 105 mins. | After 150 mins. |
| 1 | F. | ·09 | ·128 | ·108 | ·122 | ·120 |
| 2 | F. | ·102 | ·125 | ·108 | ·136 | ·105 |
| 3 | F. | ·10 | ·12 | ·13 | ·115 | ·13 |
| 4 | F. | ·104 | ·15 | ·115 | ·138 | ·125 |
| 5 | M. | ·095 | ·11 | ·096 | ·112 | ·106 |
| 6 | M. | ·12 | ·156 | ·144 | ·064 | ·122 |
| 7 | M. | ·10 | ·112 | ·117 | ·103 | ·118 |
| 8 | F. | ·10 | ·15 | ·136 | ·13 | ·098 |
| 9 | F. | ·114 | ·125 | ·143 | ·143 | ·108 |
| 10 | F. | ·106 | ·12 | ·13 | ·128 | ·09 |
| 11 | F. | ·098 | ·1 | ·116 | ·136 | ·125 |

Reference to the table will show that the effect of $\frac{1}{100}$ gr. of hyoscine hydrobromide on the blood-sugar in the normal individual is a general depression of blood-sugar values. These lowered values may be associated with a sluggish rise and fall of the curve, and it is not unusual to find a secondary rise of the blood-sugar

curve, resulting in some degree of hyperglycæmia two hours after the glucose meal and drug injection (Fig. 1).

At first sight, therefore, it would appear that hyoscine has an inhibiting action on the factors governing *both* the rise and the fall of the blood-sugar curve, but, as will be seen later, the results obtained in general with the cases of encephalitis lethargica show the same depression of blood-sugar values with *acceleration* of the fall of the curve (Fig. 5). The main effect of hyoscine on the blood-sugar curve is a depression of the glycogenolytic reaction and a variable glycogenetic response. Atropine gives a similar result, both as regards depression of the blood-sugar values and the accelerated fall in cases showing a sustained hyperglycæmia after glucose ingestion.

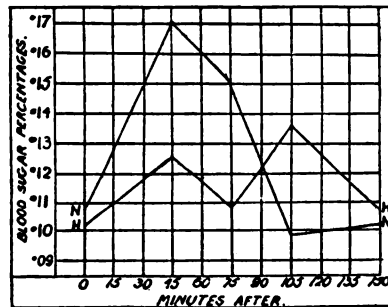


FIG. 1.—Blood-sugar curves of normal person. N, After 50 grm. glucose.
H, After 50 grm. glucose plus $\frac{1}{100}$ gr. hyoscine.

The pharmacological action of these parasympathetico-mimetic drugs is to inhibit the external secretion of the pancreas and the alimentary tract. With the general arrest of alimentary secretions the alterations in the blood-sugar curve may find explanation either in diminished or retarded rate of absorption of the sugar from the intestines, or on the lines of Allen's theories regarding treatment in diabetes, *viz.*, that, with arrest of the external secretion of the pancreas, there may be increased activity of the internal secretion with corresponding glycogenesis.

Effect of Hyoscine on Blood-Sugar Curve of the Chronic Encephalitic.

To understand the effect of hyoscine on the blood-sugar curve of the encephalitic, it is essential to appreciate that in them the blood-sugar curves after glucose alone are abnormal in type. In a recent paper, "Blood-sugar Studies in Encephalitis Lethargica" (1) we showed that encephalitic blood-sugar curves fall into three definite and distinct types. These we term Types A, B and C.

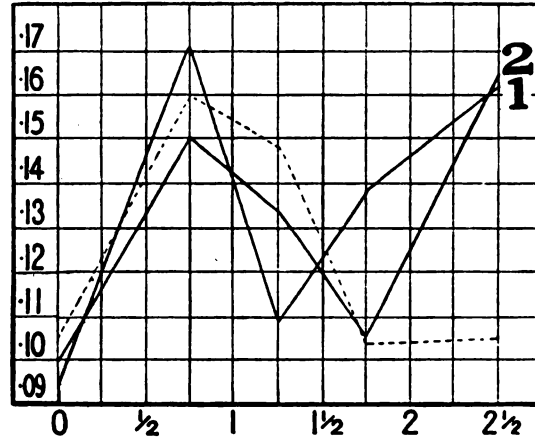


FIG. 2.—Type A. Blood-sugar curve normal in shape, but followed by a secondary hyperglycæmia. 2 cases.

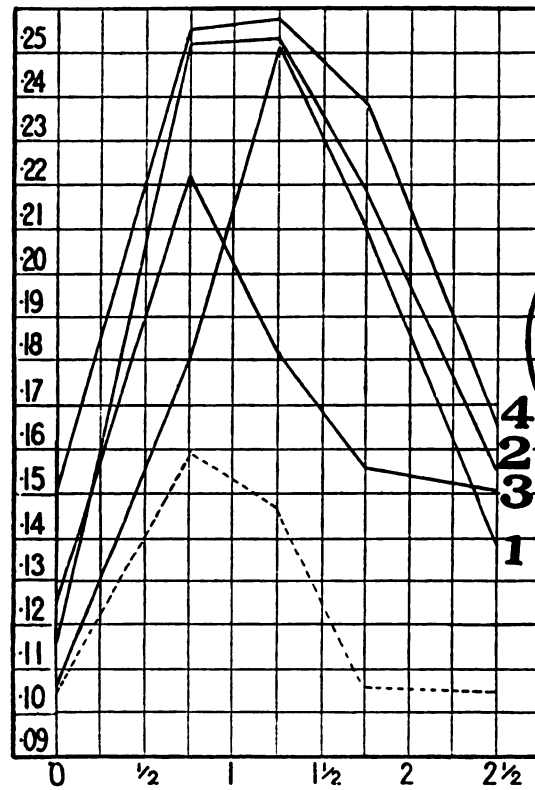
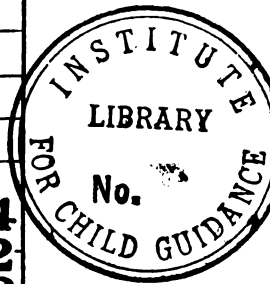


FIG. 3.—Type B. Blood-sugar curves of more or less normal contour, but with high maximum blood-sugar values.



In Type A we have a curve normal in shape, but followed by a secondary hyperglycæmia.

Figs. 2 to 4 are blood-sugar curves following 50 grm. glucose; encephalitis lethargica. The dotted line shows the normal blood-sugar curve.

In Type B we have curves with a more or less normal contour, but with high maximum levels, *i.e.*, above $\cdot 2\%$.

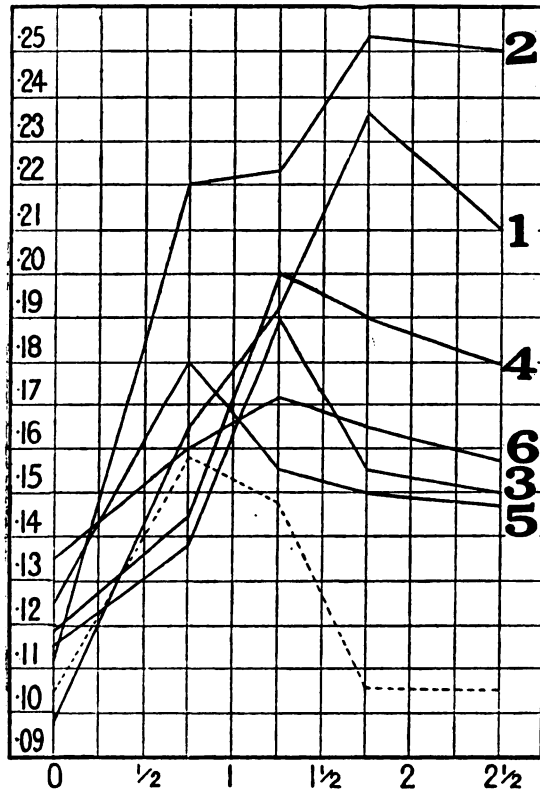


FIG. 4.—Type C. Blood-sugar curves showing sustained hyperglycæmia. 6 cases.

In Type C we have curves showing sustained hyperglycæmia.

We thus see that high blood-sugar values with a more or less sustained hyperglycæmia is the rule, and it is interesting to note that these findings are quite in keeping with the theory that we are dealing with a chronic toxæmia.

The results of the injection of hyoscine simultaneously with the glucose ingestion make it possible to classify the cases roughly into two groups.

TABLE II.—Showing the Blood-sugar Percentages in Encephalitic Patients. First, after a meal of 50 grm. of glucose, and, secondly, after a similar meal plus the injection of $\frac{1}{100}$ gr. of hyoscine hydrobromide.

| No. | Type of case. | Fast- ing level. | Glucose only. | | | | Fast- ing level. | Glucose + $\frac{1}{100}$ gr. hyoscine. | | | |
|-----|----------------------------------|------------------------|----------------|------|------|------|------------------------|--|------|------|------|
| | | | Minutes after— | | | | | Minutes after— | | | |
| | | | 45. | 75. | 105. | 150. | | 45. | 75. | 105. | 150. |
| 1 | Parkinsonian . . . | .11 | .2 | .19 | .17 | .16 | .1 | .18 | .15 | .1 | .095 |
| 2 | „ (slight). | .1 | .18 | .15 | .136 | .126 | .095 | .178 | .15 | .11 | .094 |
| 3 | „ . . . | .118 | .145 | .20 | .19 | .18 | .115 | .165 | .235 | .23 | .135 |
| 4 | „ . . . | .115 | .252 | .254 | .22 | .156 | .12 | .18 | .235 | .21 | .115 |
| 5 | „ . . . | .093 | .17 | .11 | .138 | .162 | .096 | .15 | .165 | .128 | .10 |
| 6 | „ . . . | .115 | .138 | .19 | .155 | .15 | .11 | .10 | .12 | .17 | .11 |
| 7 | „ . . . | .097 | .14 | .184 | .20 | .17 | .10 | .166 | .187 | .150 | .11 |
| 8 | „ . . . | .1 | .142 | .130 | .16 | .13 | .11 | .186 | .135 | .106 | .11 |
| 9 | „ . . . | .094 | .167 | .23 | .2 | .187 | .092 | .125 | .187 | .15 | .12 |
| 10 | „ . . . | .104 | .176 | .176 | .15 | .13 | .098 | .11 | .152 | .126 | .10 |
| 11 | Parkinsonian+apache | .11 | .186 | .176 | .15 | .144 | .1 | .17 | .15 | .13 | .11 |
| 12 | Parkinsonian . . . | .09 | .16 | .136 | .125 | .112 | .095 | .10 | .134 | .108 | .096 |
| 13 | „ . . . | .104 | .166 | .152 | .150 | .12 | .102 | .134 | .150 | .116 | .130 |
| 14 | Deluded (no Parkin- sonism) | .10 | .165 | .18 | .235 | .21 | .102 | .155 | .12 | .135 | .162 |
| 15 | Ditto . . . | .105 | .15 | .126 | .11 | .09 | .10 | .17 | .15 | .115 | .128 |
| 16 | „ . . . | .09 | .138 | .13 | .112 | .108 | .1 | .114 | .09 | .11 | .126 |
| 17 | Difficult (no Parkin- sonism) | .11 | .15 | .14 | .12 | .108 | .12 | .125 | .15 | .1 | .17 |
| 18 | Ditto . . . | .12 | .18 | .155 | .15 | .135 | .13 | .18 | .15 | .174 | .135 |
| 19 | Apache (no Parkin- sonism) | .10 | .102 | .108 | .125 | .10 | .102 | .108 | .102 | .102 | .115 |
| 20 | Depressed (no Par- kinsonism) | .11 | .22 | .225 | .25 | .25 | .115 | .17 | .22 | .155 | .21 |

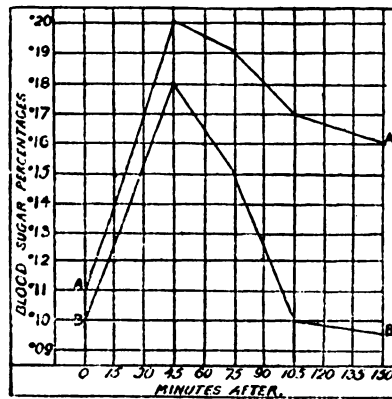


FIG. 5.—Blood-sugar curves of post-encephalitic Parkinsonian. A, After 50 grm. glucose. B, After 50 grm. glucose plus $\frac{1}{100}$ gr. hyoscine.

The first 13 cases exhibited Parkinsonism, and the effect of hyoscine on the blood-sugar curve is shown by a depression of

blood-sugar levels with acceleration of the fall of the curve, making a shape approaching the normal.

Case 13 was the only instance in which this reaction was indefinite. All the others show an "improved" blood-sugar curve and benefited clinically from the administration of hyoscine.

Seven cases (14 to 20), did not exhibit Parkinsonism, and this "improved" blood-sugar curve following hyoscine was not evident. Here there is a variable depression of blood-sugar levels, many of the cases showing a secondary blood-sugar rise, giving blood curves of the type shown to occur after hyoscine injection in the normal individual. In these cases the administration of hyoscine was not associated with clinical benefits.

The results show that in patients with chronic encephalitis, those with Parkinsonian symptoms receive most benefit from hyoscine therapy, and that this clinical improvement is coincident with an "improved" blood-sugar curve.

TREATMENT.

As a method of treatment, the hyoscine may be administered either subcutaneously or by the mouth. We have found the combined method most useful and practical. We give a hypodermic injection of $\frac{1}{100}$ gr. hyoscine hydrobromide in the morning, and follow this up with either one or two similar doses by the mouth during the day. When given subcutaneously it acts more powerfully, and its effects continue for a longer period than when the oral method is employed. The question of dosage is of importance. It is best to commence with fairly small amounts, and increase until the required effects are obtained. If given hypodermically, a start can be made with $\frac{1}{100}$ gr. once a day, and, if necessary, be increased until as much as $\frac{1}{50}$ gr. is reached. It is seldom that a larger dose than this is found necessary. When administered by the mouth, larger doses may have to be given even up to $\frac{1}{10}$ gr. three times a day, but we have never found it necessary to exceed $\frac{1}{50}$ gr. It should be given just after meals, since if taken before food the dryness of the mouth and throat makes mastication and deglutition somewhat difficult. In some cases we have found the addition of $\frac{1}{10}$ gr. pilocarpine useful in combating some of the unpleasant symptoms of hyoscine therapy, *e.g.*, the paralysis of accommodation and the dryness of the mouth.

Some of our patients have now been having hyoscine daily for over two years, and it is noteworthy that no deleterious effects whatever have accrued from the drug, and that little or no tolerance to it has developed, as shown by the fact that practically no increase of dosage has been found necessary during this prolonged period.

It should be noted that the action of the drug is merely temporary, and that as soon as the hyoscine is stopped the patient forthwith relapses into his original state. Thus we have found it essential for patients leaving the hospital for a few days to take a supply of the drug with them.

The administration of belladonna has been advocated by Prof. Hall. It, of course, belongs to the same pharmacological group as hyoscine, so that one would expect its action to be similar. We have tried it in most of our cases, and in no single instance did we find it superior to the oral administration of hyoscine, and in the majority it was of little use. These remarks apply equally to stramonium. All these drugs are, of course, merely palliative, and without effect on the progress of the disease. So far no treatment has been devised which can be claimed to be curative. We are quite satisfied in our own minds, chiefly from a clinical study of our patients, but also from pathological findings, that these cases suffer from an active disease, and it would be most unfortunate to regard them as merely exhibiting the after-effects of an acute process.

We have tried a large number of different therapies, including many of those recommended from time to time by various authorities, *e.g.*, "artificial fever treatment" by means of T.A.B. vaccine, the production of an intercurrent disease, *viz.*, hyperthyroidism by means of thyroid extract, intravenous injections of sodium cacodylate, and also sodium iodide. Two of our patients contracted erysipelas with severe hyperpyrexia, which lasted for several weeks, but no improvement in their encephalitic symptoms has so far resulted. We are satisfied that any benefits obtained by these methods are transient, and that in the majority of cases none resulted. Two other drugs which have seemed most hopeful to us are tryparsamide and argotropin, and we still continue to give them to our cases of encephalitis, irrespective of type. From experience of the drug in general paresis, we are satisfied that tryparsamide does gain access to the central nervous system in a way which no other arsenical preparation seems to do, and we therefore continue to pin our faith to it in our cases of encephalitis. What we can say is that not a single one of them has shown any further progress of his or her disease since receiving tryparsamide. We give a course of eight weekly intramuscular injections of 2 to 3 grm. The other drug which we still use is argotropin, as recommended by Wimmer of Copenhagen. This is a combination of 1% colloidal silver and 20% hexamethylene-tetramine. It is administered intravenously, one ampoule of 5 c.c. being given every other day. A course consists of 8-10 injections.

Time forbids more than the mere mentioning of other modes of treatment, *e.g.*, hot baths, massage and electricity, occupational therapy, psychotherapy, and care of the general health, all of which have their uses, but we would like to draw attention to the condition of the mouths of these patients. Pyorrhœa and other troubles are extremely common even in the youngest of them, and the correcting of these is accompanied by mental and physical improvement.

CONCLUSIONS.

1. Hyoscine is of undoubted value in the Parkinsonism of chronic encephalitis; its action is a specific one; its value is objectively demonstrable, amongst other methods, by its effect on the blood-sugar curve, which is made to approximate the normal curve.

2. It is important to remember that the action of hyoscine is only temporary, but its prolonged use does not lead to tolerance or any deleterious effects.

3. Though in the majority of cases the full benefit of hyoscine can only be obtained by hypodermic administration, there is no doubt that in many cases considerable benefit follows its oral exhibition. It is undoubtedly much superior to belladonna or stramonium in the treatment of encephalitic Parkinsonism.

4. The functional element in this disease is probably due to a lesion in or around the basal ganglia, and it has been suggested that an analogous lesion may account for similar symptoms in hysteria, chorea, Wilson's disease, etc.

5. Although no recovery can be claimed at present for the use of such drugs as tryparsamide and argotropin in the treatment of chronic encephalitis, it is hoped that time will show that they have been successful in the attack on the encephalitic virus as shown by the prevention of any further progress of the disease.

6. Oral hygiene is an important subsidiary line of treatment in the chronic encephalitic.

The authors take this opportunity of thanking Dr. Golla, the Director of the Pathological Laboratory of the Maudsley Hospital, and Dr. Norcliffe Roberts, the Medical Superintendent of the West Park Mental Hospital, for their encouragement and their unfailing interest in these investigations.

(¹) McCowan, Harris, Mann, *Lancet*, 1926, i, p. 802.