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THE RESULTS OF HIGH ATROPINE DOSAGE IN CHRONIC EPIDEMIC ENCEPHALITIS, WITH COMMENTS

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In the article on treatment of the post-encephalitic Parkinsonian which appeared in this *Journal* on September 21, 1935, reference was made to a series of cases then undergoing treatment by high atropine dosage. Since then more cases have been treated, and it has been possible to follow them up long enough to warrant certain conclusions as to its value.

For the large amount of time and trouble in carrying out the treatment and keeping records my sincere thanks are offered to many colleagues, both at public institutions and in private practice, including, amongst others, Dr. Bamford, medical superintendent, Gateshead Mental Hospital; Dr. Pool and his staff at the South Yorkshire Mental Hospital; Dr. Schneider and his staff at Rampton State Institution; Dr. E. Fretsen Skinner at the Sheffield Royal Hospital; and Professor E. J. Wayne at the Sheffield Royal Infirmary. To Professor Wayne I am particularly indebted, not only for the great trouble and interest he has taken in the cases which he has had under observation in his wards from my clinic, but also for his criticism and advice in the preparation of this paper. My part has thus been only that of a collector. At the same time any opinions, views, or conclusions which follow are mine, and I alone take responsibility for them. It has for long been known that atropine in the form of belladonna, stramonium, or hyoscyne may relieve the physical disability in some cases of chronic epidemic encephalitis, and that for this purpose doses rather larger than those laid down in the *British Pharmacopoeia* are often required. Bremer (1925) called attention to the fact that Parkinsonians showed unusual tolerance to this alkaloid, so that as much as 20 mg. a day had been given per os without the occurrence of toxic symptoms. The method known as high atropine dosage, introduced by Kleemann (1929), is based upon Bremer's observations. Since then the method has been widely adopted. It is not necessary to go into full details of this method, which can be found in the article already referred to (Hall, 1935), but some general indications will be given as to certain modifications which have been found useful.

Estimation of Optimal Dose

Kleemann (1929) begins with 0.5 mg. of atropine daily in the form of 1/2 per cent. solution of atropine sulphate given in two doses. (One drop contains 0.25 mg.) This is increased by 0.5 mg. daily, spread over three doses, so long as any objective or subjective improvement is produced (maximal dose). When this point is reached reduction should be gradual in order to fix the optimal dose on which improvement is maintained.

In many of the cases in this series this method has been followed. In some, however, after an initial small dose has been tolerated, a greater daily increase has been made without ill effects. Indeed, in patients who have previously been for some time on tincture of belladonna one may give 5 or even 10 mg. of atropine on the first day and increase by 2.5 mg. daily, not only without ill effects, but in suitable cases with rapid benefit.

Earlier observers have emphasized the necessity of keeping the patient in bed whilst estimating the optimal dose. In our experience, unless already bed-ridden, complete rest is neither necessary nor desirable after the first day or two of treatment. Even those bed-ridden at the onset should be encouraged to get up as soon as they show signs of improvement. Close daily observation of the patient is essential so long as the dosage is being increased.

In Kleemann's cases the usual optimal dose was 3 to 7 mg. atropine daily. In this series the average optimal dose was about 18.5 mg. atropine daily. The highest was 54 mg.—with definite improvement. Maximal and optimal doses, however, are not fixed points on a measurable standard, but largely dependent on two variables, the patient and the physician. In many cases, indeed, they are very difficult to assess. At any rate, the fact that 54 mg. of atropine per day can be tolerated not only without harm but with benefit shows that even the less bold prescribers need not apprehend serious danger when estimating the maximal dose. Reference will be made later to such unpleasant effects as may arise and how they may best be met.

One further point as regards the continuation of treatment after the optimal dose has been found. We have found it a convenience to prescribe the atropine in coloured tablets. Pink tablets contain 4 mg. atropine; yellow only 1 mg. By this combination of strengths it is easy to obtain any required dose of 1 mg. or upwards. The patient has no difficulty in knowing exactly how many of each colour he has to take for a dose, and this coloration distinguishes them from other less potent tablets.

Van der Meulen (1933) and others have emphasized various dangers which may occur on a sudden omission of a dose in the course of treatment. So far as this series is concerned omissions have occurred from time to time without any untoward results.

Published Records

The records of high atropine treatment published from time to time by different observers differ widely in the results obtained. At one extreme are those which claim

high percentages of complete or almost complete recoveries, at the other those in which the results have been disappointingly slight and fugitive. The greater number of records published by those who have given the method an adequate trial show results somewhere between these two extremes. They agree that in certain cases the results are extremely good, in others there is definite improvement, whilst in still others benefit is slight or absent.

In analysing the following series of cases an attempt will be made to suggest some data whereby it may be possible before advising this somewhat severe line of treatment to foretell which cases are likely to benefit and which are not.

To do this it is necessary to have some method of dividing the cases into groups. This is difficult, because the virus of encephalitis, although having a predilection for certain levels, may attack almost any part of the nervous system, and in so doing may affect some one or other part only, or several parts together to an equal or unequal extent. It may thus give rise to two broad classes of disability, which, although necessarily closely inter-mixed in effects, may be termed "psychotic" and "physical" respectively.

Classification of Physical Disabilities

A simple basis for classifying physical disability in Parkinsonism is one suggested by me in 1934—namely, the extent to which it interferes with the three acts of everyday life which mark the limit between dependence and independence. These are feeding, dressing, and moving about. The three classes of physical disability would then be:

1. Complete independence.
2. Partial dependence.
3. Complete dependence.

In Class 1 may be placed those who can feed and dress themselves and walk about without assistance. They may be very slow at their meals; there may be some shakiness. They may have oculogyric attacks or torsion spasms. Their gait may be abnormal, they may even fall over at times, but *they do not require physical assistance*. They can look after themselves.

Class 3 is also clearly defined. They can neither feed nor dress themselves; they cannot walk without help; indeed in some cases they cannot even turn over to change their position in bed, but have to call for help in order to do so.

Class 2 necessarily includes persons who differ widely in the amount of their physical disability. Some can walk without help, but cannot feed themselves on account of tremor. Others can feed and dress themselves, but cannot walk without help, and so forth. In other words some are almost independent, others largely dependent.

These three classes of physical disability are not necessarily consecutive. Although the tendency is for the Parkinsonian to become gradually more helpless as time goes on, yet this is not always so. There are cases which remain in Class 1 year after year and show no tendency to get worse; others who quite early in their illness were in Class 3, but owing to treatment of various kinds have returned to, and remain for years in, Class 1 or Class 2.

Classification of Psychotic Disability

To classify "psychotic disability" is more difficult. The forms in which it may show itself are too numerous and too complex to serve as a basis. For practical purposes,

however, it is convenient to make two groups, according to the extent to which it dominates the clinical picture. Thus into Group A are placed those in whom psychotic disability may be said to be "primary or predominant," and into Group B those in whom it is "secondary, or so slight as to be negligible." This or any such arbitrary grouping is necessarily very imperfect. Usually, however, there is little or no difficulty in deciding to which group a particular case belongs.

In most of the cases under certificates the predominance of psychotic disability is obvious. On the other hand, in a certain small number of certified patients, especially those in whom "physical disability" is advanced, the "psychotic disability" has either always been secondary to the physical disability or though originally predominant has become less so with the increase of the latter.

By combining the degree of psychotic and physical disability present in each case it is possible to classify the encephalitics in the following way:

Psychotic Disability	Physical Disability
Group A : Marked	(1) Independent
"	(2) Partially dependent
"	(3) Wholly dependent
Group B : Slight or absent	(1) Independent
"	(2) Partially dependent
"	(3) Wholly dependent

In the fifty-eight cases here recorded this form of classification has been adopted, and, as will be seen from the results, the benefits obtained from large doses of atropine have been very different in the different groups.

TABLE I.—Fifty-eight Cases of Chronic Epidemic Encephalitis Grouped According to their Disabilities

Psychotic Disability	Physical Disability	No. of Cases
Group A : Marked	(1) Independent	26
	(2) Partly dependent	8
	(3) Wholly dependent	10
Group B : Slight or absent	(1) Independent	4
	(2) Partly dependent	2
	(3) Wholly dependent	8
		58

The larger number of cases in Group A is due to the fact that opportunities for carrying out observations such as these necessarily offer themselves more readily at mental hospitals, where there are many such cases and the requisite control is possible.

The results are given in three categories—namely:

- (a) Great improvement.
- (b) Definite improvement.
- (c) Slight or no improvement.

TABLE II

Classification		Improvement		
	No. of Cases	Great	Definite	Slight or None
Group A : (1)	26	0	5	21
" (2)	8	0	2	6
" (3)	10	2	2	6
Total ..	44	2	9	33
Group B : (1)	4	0	3	1
" (2)	2	1	1	0
" (3)	8	6	2	0
Total ..	14	7	6	1

Cases Greatly Improved

It is seen that in nine cases (three men and six women) the improvement is described as "great." Such a term hardly does justice to the facts; it might well be called "extreme."

In each of these cases the person, who had been practically bed-ridden and required help in almost every act of daily life for a long period (in some cases years), was, as the result of treatment, not only able to be up and about but also to take part in and enjoy social life again. The following is a short account of four of these cases:

Case 41: Female, aged 49.—Acute attack in 1919. In 1921 Parkinsonism developed with stiffness and tremor of the right arm and leg. There was never any excessive salivation. Mental symptoms took the form of a somewhat childish emotional psychasthenia. In 1925 treatment by belladonna was begun, and 20 minims of the tincture was taken three times a day. On this she improved very considerably. Exactly for how long or how regularly this treatment was continued is not recorded, but the history of the next few years shows that it was not continued regularly and the doses were diminished. In 1933 there was considerable mental depression. The Parkinsonism was much more marked. She was unable to walk by herself, although not actually bed-ridden. She was unable to write even her own name on account of the continuous tremors. At that time she was taking 10 minims of tincture of stramonium three times a day. High atropine dosage was begun in July, 1935. In August she was taking 13 mg. of atropine per day, and the improvement was very great. The tremor in the legs had largely disappeared, and was so much less in the right hand that she was able to write a letter without any recognizable tremor in the handwriting. More than a year later, in January, 1937, she can walk a mile without difficulty, play on the piano again, and sew and knit. She has lost her mental depression, and is brighter and happier than she has been for many years. The daily dose of atropine is 10 mg. given in four equal doses.

Case 54: Female, aged 29.—Bed-ridden for four years, unable to feed herself or to walk without assistance. Speech almost inarticulate. Marked hypertonus. Optimal dose of atropine, 30 mg. per day. Condition after four months' treatment: she is up and about, can feed and dress herself, takes part in domestic work, goes out for long walks, and dances.

Case 57: Female, aged 41.—Acute encephalitis in 1921, followed by Parkinsonism. During the last few years she has been completely dependent, requiring to be fed, dressed, and helped to walk only a few steps. In March, 1936, high atropine treatment was begun. The optimal dose was 42 mg. The following is an extract from a letter written early in 1937 by the patient herself—that is, about a year after treatment was begun. The handwriting does not show any trace of Parkinsonism. "I could not walk a hundred yards without holding someone's arm, and could not feed myself or help myself in any way. Now I can walk three miles quite alone, feed myself perfectly, take off my own coat, etc. . . . I am so much better that I hardly know myself."

Case 52: Male, aged 30.—Bed-ridden for five years, had to have help in feeding and walking. Speech almost unintelligible. Salivation excessive and continuous. Severe tremor of both arms and legs. Optimal dose of atropine, 30 mg. a day. Condition after four months' treatment: up and about every day, looks after himself, helps in housework, goes to "pictures" and entertainment. Takes a pride in his appearance. Tremor much less.

At first sight a record of "great improvement" in only nine out of fifty-eight cases does not seem to compare favourably with some of the results published elsewhere. If, however, it is realized that in this series there were only seventeen whose physical disability had reached Class 3 the percentage of "great" improvements among these becomes considerable.

In Table II it will be noticed that of these nine cases of "great improvement" seven belonged to Group B—that is, their psychotic disability was not predominant, whilst their physical disability before treatment was Class 2 or Class 3.

Unless the physical disability is considerable before treatment is begun it can hardly be said to improve "greatly." All such striking and dramatic improvements as have been from time to time recorded must have been Parkinsonians of Class 3 or the more dependent cases of Class 2, such as Case 41 of this series, who had to be placed in Class 2 because she was not *completely* dependent, yet her dependence on others before treatment was almost complete and her improvement could only be described as "great."

But if atropine is so effective in relieving serious physical disability (Class 3) why did it fail in six cases in Group A (3)? In four of them (Cases 6, 22, 34, and 38) the answer is easy. Long-standing Parkinsonism had in each of them led to deformities of the arms, legs, and trunk of such an advanced kind that a return to useful conditions was impossible. In the remaining two cases (Nos. 16 and 31) there was no such deformity. In them the lack of improvement was due to the predominant psychotic disability. Both were very impulsive. Neither of them would co-operate. In this connexion a word must be said about Case 42, one of the B (3) group, whose improvement was not so great as expected.

This girl had been leading the life of a complete invalid for some years at the home and under the care of a devoted relative, who had done everything for her. She was very emotional and would not co-operate in anything that required effort on her part. She had become so accustomed to invalidism and the daily routine of doing nothing whatever to help herself that she would rather remain *in statu quo* than undergo any treatment which involved the least personal discomfort.

Indeed this question of lack of co-operation is by no means uncommon in Parkinsonians of Class B (3), in whom there is a considerable psychotic element.

In fairness to the method, however, it must be admitted that in most of these there was some slight improvement; thus the records state:

Case 6.—Speech a little better, saliva a little less, can move about in bed a little more easily.

Case 38.—Able to help himself a little in feeding. Speech rather clearer.

Case 22.—Oculogyric attacks have ceased since treatment.

Case 42.—Rigidity and tremor rather less, speech more intelligible.

As regards the thirty-four patients in whom psychotic disability was marked (Group A), and physical disability less, (1) and (2), "great" improvement is not recorded in any, and even improvement which could be called "definite" in a small number only.

These results are in general agreement with those obtained by other observers. It is the general experience that the mental condition of these patients, except as in so far as it is secondary to the distressing physical disability, is not improved to any extent by atropine treatment.

Psychotic disabilities, however, vary so widely in character that it is impossible to generalize. Busse (1932) in a report on 130 cases thinks that it has a definite action on impulsive disorders but no effect on hyperkinetic psychomotor cases. He finds that it may relieve quarrelsomeness by diminishing motor rigidity. Lisak (1932) finds that it has no beneficial effect on character changes. In the mental depression secondary to the physical dis-

ability, however, improvement is often marked, as is shown above in the letter written by Case 57. Indeed, to return from complete helplessness to ordinary life sometimes produces a condition of euphoria.

Special Symptoms

Salivation.—This is the one condition that should always benefit from full doses of atropine, and indeed even when troublesome will often improve on much smaller doses of atropine, such as are contained in the B.P. doses of tincture of belladonna. It is, however, by no means a constant symptom. It may be completely absent, even in advanced cases, whilst in others much less advanced it is a serious source of annoyance.

Oculogyric Attacks.—These were present in twenty-two of the cases. In five there was no improvement. In twelve the attacks were less frequent after treatment. In five it is recorded that they had ceased entirely. There seems no doubt that under high atropine treatment these troublesome attacks may cease entirely, at any rate for long periods. Their frequency and severity, however, vary so widely in the same individual from time to time, and are so readily influenced by emotional and other psychical happenings, that it is always difficult to be sure that they are permanently arrested or to name the exact agent which has stopped them for the time being. Though not merely a hysterical phenomenon, yet, in those liable to them, excitement, correction, or having to do something they do not like will readily bring on an attack, while sufficiently strong suggestions of various kinds may prevent them or stop one that has begun. In one man (Case 25) an observant attendant in charge of the patient assures me that the attacks have been much less frequent since the patient was not allowed to lie down when one threatened to come on.

Discomforts Early in Treatment

Various discomforts were complained of in the initial stages of the treatment, but on the whole they were few and capable of relief. Among these were:

Occasional mental confusion or slight delirium coming on shortly after taking the drug and lasting sometimes for an hour or two; in some cases temporary loss of memory and occasionally vertigo. Drowsiness about two hours after a dose has also occurred.

Visual disturbance due to paralysis of accommodation is common and tends to cause annoyance or even alarm. This can be relieved temporarily by (1/2 per cent. solution of eserine) drops in the eyes, and later by glasses adapted for complete loss of accommodation. In any case with a suspicion of glaucoma the treatment is contra-indicated.

Dryness of Mucous Surfaces.—Dryness of the mouth and throat occurred in a few cases and gave rise to difficulty in swallowing. Dryness of other mucous surfaces besides the mouth may cause discomfort. Thus in two women there was irritation about the vulva and in one man troublesome priapism. One patient complained of constipation with undue dryness of the anus. All these were relieved by a simple ointment.

Gastro-intestinal upsets in the form of vomiting and acute diarrhoea occurred in a few cases. They were, however, only occasional, and were relieved by ordinary measures without stopping the atropine.

Difficulty in starting micturition was observed in one or two of the men, but was not of serious importance, nor did it call for special treatment.

Hyperthermia during Treatment

A certain number of observers have recorded occasional rises of temperature during the taking of large doses of atropine. Such an occurrence after atropine has long been recognized by pharmacologists. According to Cushny (1936) "atropine often induces a marked rise in temperature, the cause of which cannot be said to be definitely known. According to Ott the dissipation of heat is increased, but the heat formation undergoes a still greater augmentation." Sollmann (1936) says, "Atropine suppresses perspiration and thus causes a rise of temperature with moderate doses, notwithstanding the cutaneous vasodilatation. . . . Larger doses produce a fall of temperature with lessened heat production." Dixon (1936) says, "It is not uncommon to find a small rise in temperature after taking a large dose of atropine. This is probably a direct action on the thermogenic centre. It cannot be due to a diminished loss of heat because the amount of heat dissipated is actually increased. In severe cases of poisoning the temperature rises sometimes very high, even to 107° or 108° F. It is this rise in temperature which is responsible for the vasodilatation of the skin vessels; it is an attempt on the part of the nerve centres to lower the temperature by increasing the loss of heat." It is evident that, as Cushny says, the cause cannot be said to be definitely known.

It was observed in four cases of this series. In three of these (Nos. 1, 2, and 3) the circumstances are of especial interest in connexion with the above opinions as to its cause. These men were all in the same ward, and in each the dose of atropine had reached a considerable height (33.5 mg. daily). A sudden spell of very hot weather had occurred in August, the ward thermometer registering 78° F. Each man's temperature went up to 104° F. or rather higher. There was no discomfort other than thirst, and in each the temperature was easily reduced by sponging. It seems probable that a contributory cause in these three cases was an inhibition of sweating due to the atropine. In this connexion it is of interest to recall that more than one fatal case of hyperpyrexia has been described in chronic Parkinsonians. Astley Cooper (1936) mentions a fatal case of heat stroke apparently "due to failure to move out of the sun," and he adds (I think pertinently) "combined with stramonium medication."

In one of the fatal cases with hyperpyrexia (temperature 109° before death) which I recorded in 1935 the question of it being really a heat stroke due to exposure had not occurred to me until reading Astley Cooper's paper. Inquiry, however, in my case showed that this man also had been sitting in the sun without moving for most of a day, which happened to be exceptionally brilliant and hot. About 5 p.m. the attendant noticed that he looked ill. He was put to bed and found to have a temperature of 105°. In spite of treatment the temperature rose steadily, drowsiness increased to coma, and before death at 7 a.m. next day the temperature had reached 109°. This man also was taking stramonium in full doses, and had been doing so for some time.

These two cases taken together suggest that in persons under the influence of atropine in any form, whatever may be the explanation, the possibility of dangerous hyperpyrexia on exposure to a heat considerably less than affects normals must not be overlooked.

Occupational Therapy

Among those who have obtained the best results from high atropine treatment the importance of supplementing it by various forms of mental and physical treatment is generally agreed. This cannot be too strongly emphasized. In the early cases recorded by Kleemann (1929)

baths of various kinds, massage, and physical exercises formed a conspicuous and valuable feature of the treatment. At institutions where there are numbers of Parkinsonians such measures are more easily carried out, although remedial baths, massage, and machines for exercising are not available for treatment in this country as widely as in Germany; yet it is not the exact physical nature of the supplementary treatment which matters so much as the suitable and regular occupation for mind and body. This can be carried out at any institution provided it is organized and supervised. Simple domestic duties, easily devised occupations graded to suit the capacity of each individual, games, physical drills, and competitions are quite as valuable as baths or massage, if not more so.

In private cases where treatment has to be carried out under home surroundings this "occupational therapy," using the term in its widest sense, is often more difficult. It is not uncommon to see one of these patients after improving greatly in hospital go steadily back to his former condition on returning home, even if atropine treatment is continued.

The importance of "environment" cannot be too strongly emphasized. All that the atropine does is to release the brake in the Parkinsonian's musculature. What use will be made of it depends upon what there is to do and what encouragement to do it.

There is still one other factor of great importance, whether the treatment is carried out at an institution or in the private house—that is, the personal will power of the individual himself, upon which the effect of treatment largely depends. Without full co-operation it is impossible for benefit to be obtained, or if attained maintained.

In some of the records published in Germany many of the cases are said to have left the institution fit for work (arbeits-fähig) as the result of high atropine dosage. In most of these it would seem that the Parkinsonian disability must have been only (1) or (2), and the psychotic disability Group B. If so, in our experience a similar result would probably have been obtained by much smaller doses of belladonna or stramonium.

But once a Parkinsonian always a Parkinsonian, and whilst the physical disability may have been so much relieved by treatment as to make the patient fit for work, very few are in a condition to compete with normal persons in the labour market.

Summary

1. Treatment by very large doses of atropine (high atropine dosage treatment) causes remarkable improvement in certain cases of post-encephalitic Parkinsonism.

2. The greatest benefit is seen in cases in which the disability arises chiefly from muscular stiffness and excessive flow of saliva.

3. Improvement may also occur in tremor, in the frequency of oculogyric attacks, and in various spasmodic symptoms. In these, however, it is less in amount and more variable.

4. Cases in which psychotic disability is predominant and Parkinsonism is either absent or only slight do not usually show much benefit from this form of treatment. Where the psychotic disability is largely secondary to the physical disability removal of the latter by high atropine dosage may be accompanied by definite improvement in the former.

5. Under no circumstances does the Parkinsonian syndrome completely disappear; and unless the treatment is

maintained and reinforced by suitable environment, using the term in the widest sense, there is usually a rapid return to the pre-existing condition.

Concluding Remarks

Where physical disability is maximal and psychotic minimal (Group B 3) treatment by very high doses of atropine is capable of producing results of a remarkable kind, provided that the physical disability has not caused serious deformities, and that there is full co-operation on the part of the patient. Conversely, where psychotic disability is maximal and physical minimal (Group A 1) it is not likely to be of much benefit. The fact that some cases not only tolerate massive doses but do not begin to improve until they are reached, whilst others improve on doses within or but little beyond the limits given in the *Pharmacopoeia*, suggests a quantitative factor in its action.

Its administration in massive doses is unnecessary in those cases of chronic epidemic encephalitis in which it is not likely to be of service, and uncalled for in any case until ordinary doses have been tried and failed. Otherwise there is a danger of bringing discredit on the most efficient agent we possess in relieving some of the disabilities of Parkinsonism.

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A. Hautant (*J. Laryng.*, February, 1937, p. 65) describes certain lesions of the larynx in which a differential diagnosis may be extremely difficult or almost impossible. In general, tuberculosis of the larynx can be easily distinguished from cancer by the following characteristics. Laryngeal tuberculosis does not fix the vocal cords; it is accompanied by lung lesions and there are tubercle bacilli in the sputum; in histological sections giant cells are seen. The exceptional cases where diagnosis is difficult are said to fall into three groups. (1) Unilateral tuberculosis, localized in the subglottic region. (2) Tuberculous tumour of the ventricle with quiescent pulmonary tuberculosis. (3) Cancer simulating tuberculosis owing to its situation and aspect. The author gives clinical examples belonging to each group with many excellent illustrations and diagrams. One of the photomicrographs shows a tuberculous giant cell in contact with a deep epithelial cord of a carcinomatous nature. The association of tuberculosis and cancer in the same laryngeal lesion has very rarely been observed. With negative findings in the lungs and sputum the limited tuberculous tumour may be confused with a simple neoplasm. In such cases the tuberculous mass sometimes invades the cartilage and fixes one cord; confusion with cancer is then almost certain. In the event of the diagnosis as between tuberculosis and cancer remaining uncertain, active laryngeal treatment must be carried out with extreme caution. An untimely surgical operation might cause a fatal attack of acute tuberculosis. Hautant relies a good deal on side-view radiographs of the larynx, a method of investigation which appears to be little used in this country. One can see the outline of the thyroid and cricoid cartilages and shadows of tumour masses within those outlines.