The chemical character of the base may be an important factor; lard and wool-fat are both esters and both absorb well, the absorption increasing on continued rubbing, so that probably part at least of the absorption takes place through the sebaceous glands. Possibly the difference between them in the absorption of medicament may be due to the glyceryl esters of the lard, which may assist the secretions of the glands to form oleates or other easily absorbed compounds; the oleate, as shown above, is itself easily absorbed. The cholesteryl esters of the wool-fat may not form similar compounds. It has been generally assumed that the wool-fat would be the better base for absorbent ointments because it approximates more nearly to the natural fats of the skin; though this may be an important factor in the absorption of the wool-fat itself, it evidently does not aid the absorption of the mercurial medicament.

Paraffin composed of hydrocarbons and comparatively inert chemically is not likely to form compounds with the sebaceous secretions; it has not much power of penetrating the skin, and possibly that which is absorbed may be taken up by the epidermal layers; the fact that absorption does not increase with increased rubbing seems to point to this possibility.

One factor undoubtedly influencing the amount of absorption by the skin is the temperature; it was always found that rubbings done in very cold weather gave less absorption than usual. This may be partly due to the increased vascularity of the skin at the higher temperature, and partly to the higher temperature making the ointment softer and more easily rubbed into the skin. That the latter is not the only explanation is shown by the fact that rubbings taken on an exceptionally hot day in July, 1923, gave figures slightly below the average—namely, 10 per cent. for a lard and 5.5 per cent. for a paraffin base. Possibly the moist condition of the skin from perspiration on that day had an adverse influence on absorption.

An attempt was made to compare the amount of absorption through the skin of the palm, which contains no sebaceous glands but many sweat glands, with the amount absorbed through an equal area on the arm. The rubbings were carried out on the palm and the arm on the same day, and the same mercurial ointment with a lard base was used. The total absorption through the palm was 4.3 per cent., and through the arm 7.3 per cent.; the amount of mercury absorbed in the palm was 0.8, and through the arm 1.8; the lessened absorption through the palm may be due either to the greater thickness of the epidermis or to the absence of sebaceous glands, or more probably to both of these factors.

CONCLUSIONS.

1. Under the conditions of these experiments it was found that when rubbed into the skin all mercurials were absorbed to some extent from all the bases tested.
2. That in all cases the greatest absorption took place from the lard basis, and that the amount of absorption with the lard basis increases more with a prolonged rubbing than with other bases.
3. That hydrous wool-fat was absorbed to a greater extent than lard, but that the mercurial was not absorbed with it, so that the absorption of mercury was actually less than from a lard ointment of equal strength.
4. That the absorption from a paraffin base was always less than from a lard base.
5. That the amount of mercurial absorbed was proportional to the amount of mercurial in the ointment, at any rate up to 30 per cent. of the mercurial.
6. Of the different mercurials examined the mercuric oxide was the most readily absorbed, either as an ointment or in the form of the official oleate. This, however, is not suitable for use when the general absorption of mercury is desired, as ointments containing over 10 per cent. of the oxide cause considerable irritation of the skin.
7. Ammoniated mercury and mercury salicylate were absorbed almost as well as the oxide. Calomel was absorbed to a less extent than any of the other mercurials examined.

8. Metallic mercury was absorbed rather less than the oxide, but can be used in stronger concentration without causing undue irritation of the skin. The official mercurial ointment with a lard base seems to be the best preparation for ensuring the general absorption of mercury. The inunction of 4 grams (about 1 drachm) for two minutes gave, on an average, an absorption into the body not exceeding 0.12 gram (about 1.84 grains) of mercury, and after ten minutes' inunction an absorption not exceeding 0.17 gram (about 2.61 grains).

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THE TREATMENT OF POST-ENCEPHALITIC PARKINSONISM BY NICOTINE.

BY

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THE use of tobacco in various modes, internally as well as externally, for the purpose of relaxing muscular action in diverse forms of disease, was in vogue some sixty years ago.⁶ In view of this and our present knowledge of the action of nicotine on the preganglionic cells and that of the sympathetic on muscular tone, I decided to try it in the treatment of a series of cases of post-encephalitic Parkinsonism. Although it did not lead to any permanent cure of the disease, it had an undoubted beneficial effect, which, although only temporary, was sufficiently encouraging to merit further consideration and trial.

Parkinsonism, a very frequent sequel of encephalitis lethargica, is recognizable by the typically expressionless face, the staring look, the monotonous voice, the stiff and shuffling gait, the short steps by which the patient moves, holding the arms motionless by his side. Other common symptoms are sialorrhoea and a rise of the pulse rate.¹ The retraction of the eyelids (which gives rise to the peculiar stare), the sialorrhoea, and the rise of the pulse rate all point to sympathetic stimulation, and it is reasonable to suppose that the increase of muscular tone may be produced in a like manner.

Hunter has remarked how the rigidity exhibited in post-encephalitic Parkinsonism conforms in all its characters with that due to an excess of plastic tone. It is diffuse, the selective incidence of the muscles is absent, and the resistance to passive movements is the same throughout all the range of movement. Moreover, there is a tendency to fixation of the limbs in any posture passively imposed on them, and poverty and slowness of voluntary movement.² In some very interesting experiments on birds he observed that the removal of the corpus striatum gave rise to diffuse muscular rigidity of the wing remarkably similar to the Parkinsonian rigidity in man. He concluded that the corpus striatum in man, with the cortex intact, might possibly control through the intermediation of subpallidal nuclei, as the substantia nigra, the sympathetic prespinal reflex arc subserving the plastic tone.³

Many observers have described, in cases of encephalitis lethargica of the Parkinsonian type, profound degenerative changes in the cells of the substantia nigra in the mid-brain and calcareous arterial degeneration of the anterior part of the globus pallidus of the lenticular nucleus, sometimes accompanied by thrombosis of the affected vessel.⁵

Lesions of these higher centres may possibly interfere with the normal control of the prespinal reflex arc, an increase of plastic tone thus resulting in the same manner as a lesion of the upper motor tracts leads to an increase of contractile tone which is subserved by the somatic reflex arc. Nicotine, inasmuch as it paralyzes the preganglionic

sympathetic cells, may block the sympathetic prespinal arc at (A) and in this way reduce the plastic tone (Fig. 1).

The theory that tonus may be divided into "plastic" and "contractile" elements has received new support from the work of Hunter and Royle. According to this theory there would be two kinds of fibres in the striated muscle

FIG. 1.—The corpus striatum and the substantia nigra, the centres chiefly involved in post-encephalitic Parkinsonism. The arrow marks the site where nicotine blocks the prespinal sympathetic reflex arc. 1, Afferent sensory nerve. 2, Preganglionic sympathetic cell. 3, Efferent sympathetic cell. 4, Sympathetic ganglion. 5, Posterior root ganglion. 6, Ponto-spinal tract. 1-6, Prespinal sympathetic reflex arc.

of vertebrates distinguished by contrasted morphological and physiological properties: large fibres innervated by medullated (or somatic) nerves, and slender fibres innervated by non-medullated (or sympathetic) nerves. The fibres receiving somatic nerve endings are responsible for the contractile tone, whilst the other set of fibres innervated by the sympathetic system exhibit plastic tone. The latter are comparable to the fixing muscles of invertebrates and take part in fixing the length of the muscles exhibiting contractile tone.⁴

The cases of post-encephalitic Parkinsonism which may be expected to benefit from treatment by nicotine are those where voluntary muscular control is intact but movement is hampered by excessive plastic tone. By depressing and subsequently paralysing the sympathetic nerves with the drug, we attempt to eliminate the plastic tone and free the limbs from spasticity.

Nicotine was administered by hypodermic injections, the pure alkaloid being used. Signs of intolerance, such as nausea and vomiting, fainting, and tachypnoea, were carefully watched for, and for this reason the patients were kept in bed throughout the whole course of treatment.

The pulse rate, respiratory rate, and the blood pressure were recorded immediately before and after the nicotine injections. The estimations were carried out at half-minute intervals for three minutes and at minute intervals for a further seven minutes. The commonest type of response was characterized by an initial fall in the pulse rate, followed by a rise, with a return to normal within seven to ten minutes (Fig. 2). This was found in 60 per cent. of cases. In 30 per cent. there was no initial slowing of the pulse. The rise of the pulse rate was in many cases well marked, with an average increase of 20 beats a minute and with a maximum of 40. The rise usually took place one and a half minutes after the injection and reached a maximum height in two to three minutes. The initial slowing of the pulse seldom lasted more than two minutes. The blood pressure in 40 per cent. of cases showed a gradual rise of both the systolic and diastolic pressures, followed by a return to normal within ten minutes, but in 25 per cent. there was no response, and in the remainder it was quite irregular. The respirations in half the cases

showed an initial quickening, followed by a slowing of the rate; in the remainder the response varied, the secondary fall being often absent.

Following nicotine injections other phenomena were noted, such as flushing of the face, profuse sweating, tremors, thirst, nausea, vomiting, and tachypnoea. In two cases a fit occurred a few minutes after the nicotine injections. In one case the fit followed an injection of 1/10 grain, and was characterized by twitchings of the mouth, tonic spasms of the arms and legs, and incontinence of faeces and urine; it lasted a few minutes. In the second case the patient tolerated three doses, each of 1/10 grain, but after the fourth suddenly had a fit, with tetanic spasms of the hands, cyanosis, and profuse sweating, and was unable to speak for two minutes. Vomiting followed the fit.

With the help of the pulse, respirations, and blood pressure charts it was possible to check the action of the nicotine and to measure the degree of tolerance of each patient to the drug. An initial dose of 1/30 grain was given thrice daily at the beginning of the treatment and continued for a few days. If at the end of this period the pulse chart did not show any appreciable change the dose was increased. Such a procedure was adopted every time the dose was increased until the full dose was reached. This varied between 1/10 and 1/5 grain thrice a day, and was always followed by a well marked rise of the pulse rate of at least 12 to 20 beats a minute. The patient was afterwards kept on the full dose for two to three weeks or until symptoms of intolerance set in. In many cases, however, it was found that nausea and vomiting promptly disappeared after the dose had been repeated a few times, and that the treatment could be continued.

A series of 13 cases of post-encephalitic Parkinsonism have been treated in this way with nicotine. Every case presented the typical signs and symptoms of Parkinsonism, which in most cases were of several months' standing.

All the cases had a history of an attack of "flu" or of a pyrexial disease with the typical accompaniments, such as diplopia, headache, and vomiting which revealed that the illness had been an attack of encephalitis lethargica. The attack either marked the beginning of their present state, into which they had gradually crept, or was definitely separated from it by a latent interval of nine to twelve months or even longer. In one case there was a definite history of head injury preceding the onset of Parkinsonism.

Of the 13 cases, 9 showed an improvement after nicotine treatment, whilst 4 were unaffected. Of the latter, one proved later on to be a case of true Parkinson's disease. The improvement in some cases was really striking. The patients volunteered the statement that they were feeling better because "their joints felt looser" or because "their limbs were freer."

A man, aged 30, a 'cello player, in February, 1921, had an attack of encephalitis with diplopia and delirium, followed by drowsiness of three months' duration. For the last four years he had been complaining of neuralgic pains in the legs, of

FIG. 2.—Charts of the pulse rate, blood pressure (systolic and diastolic), and respirations taken immediately before and after an injection of 1/5 grain of nicotine. The pulse chart shows an initial slowing followed by a rise, the rate returning to normal within ten minutes.

periods of sleeplessness, and of impairment of memory. In April, 1925, he developed a tremor and stiffness of the fingers of the left hand, which seriously interfered with his playing. He underwent a fortnight's course of nicotine treatment, the dose being gradually increased from 1/30 grain to 1/10 grain thrice daily. A further increase to 1/5 grain thrice daily was tried, but had to be stopped because it caused vomiting. The patient was discharged much improved; although the mask-like expression was still present the movements of the limbs were much freer and the gait steadier. The patient thought that he would be able to play the 'cello again, and, when seen a month later, stated that he had resumed his work and that he was feeling much better.

A youth, aged 17, had an acute attack of encephalitis lethargica in April, 1924, with diplopia, squint, headache, and delirium, followed by lethargy. He recovered completely and felt quite well until February, 1925, when all the movements commenced to be slow and required a great effort on the patient's part. When I saw him in May, 1925, he was an obvious case of Parkinsonism, with the typical facies, rigidity of the limbs, and marked retropulsion; he would commence to sway backwards, and in order not to fall would start walking backwards, and continue to do so until arrested by a wall or by falling. He underwent nicotine treatment for three weeks, with increasing doses up to 1/10 grain thrice daily. At the end of this course of treatment he had greatly improved; the back-stepping gait had disappeared, and he walked briskly, swinging his arms alongside of him. The expression in his face had also returned, and he could smile normally.

The tone of the muscles was repeatedly examined before and after the nicotine injections, and more especially the capacity of the limb (brought by a passive movement into a new posture), when released, to remain in that new posture. Such a property Sherrington has termed "plasticity" of the musculature, and was measured by him by means of the "shortening and lengthening reaction." Thus, if the leg be flexed at the knee, so lengthening the extensor muscles of the thigh, this position is retained ("lengthening reaction"); if the knee be now extended, so shortening the extensor muscles, the new position is again maintained ("shortening reaction").

The "shortening and lengthening reaction" was found in many cases to be definitely diminished after the nicotine injections, and in some it disappeared entirely after the course of treatment.

A man, aged 39, in January, 1924, had a dizzy attack whilst at work, followed by diplopia and drowsiness. He recovered completely from his illness, and was quite well for seven months. Six weeks before his admission to the hospital he gave up his work because of his inability to use his tools or to wheel a barrow. He presented a typical Parkinsonian syndrome, with mask-like face, marked stiffness of the muscles of the neck, and loss of lateral rotation of the head when looking sideways. "Shortening and lengthening reaction" of the upper limbs was well marked, and sialorrhoea was present. He received nicotine treatment for three weeks, the dose ranging between 1/30 and 1/10 grain thrice daily. At the end of the three weeks the stiffness of the neck muscles had disappeared, and likewise the "shortening and lengthening reaction" of the upper limbs. The sialorrhoea was, however, unaltered.

Nicotine had no effect on either the tremors or the sialorrhoea. The persistency of the tremors in some cases masked the improvement of the patient's stiffness, so that no real relief was obtained, and the patients would complain of not feeling better because the tremors had not improved. In one case the phenomenon known under the name of "kinesia paradoxa" was observed. A girl, aged 15, who had been undergoing treatment for a fortnight, was seen one day to run up the stairs as if her fetters had suddenly fallen off, but shortly afterwards relapsed into her Parkinsonian state. Some cases showed a marked improvement one week, only to fall back worse than ever the next. Any improvement of this kind was ascribed to the sudden variations and to the spontaneous recoveries so commonly seen in this disease, and not to any therapeutic effect of nicotine.

In observing the patient's progress allowances were made for improvements which might have been caused by suggestion; leading questions were therefore purposely avoided, and objective findings, such as a definite diminution of tone, a return of facial expression, or an improvement of the gait, were taken to be of more importance than subjective ones. All the patients were seen again six months later. The cases which had benefited by nicotine treatment had all relapsed into their previous state, and a case which had not responded to it had died. In one case the improvement lasted a month, after which the patient felt as bad as ever. In another the relapse occurred after only a week, and was ascribed to a sudden bereavement in the family.

In concluding, I may say that treatment by nicotine failed to give any permanent cures, although the immediate results were indisputable. The treatment should therefore be repeated at frequent intervals, say, of two to three months. Nicotine had an undoubted action in reducing muscular rigidity, and this was ascribed to the paralyzing effect of the drug on the prespinal reflex arc subserving plastic tone, thus throwing new light on the dual nature of muscular tone and adducing fresh evidence that one element of muscular tone is under the control of the sympathetic nervous system.

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AN EXPLANATION

OF

THE TWO FORMS OF BILIRUBIN DEMONSTRATED BY THE VAN DEN BERGH REACTION.

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To Ehrlich is due the discovery of the fact that bilirubin in acid-alcoholic solution couples with diazotized sulphanilic acid to form a dyestuff, azobilirubin. Van den Bergh has applied this reaction to the detection of bilirubin in blood serum, and hence to the clinical study of jaundice. He made the important observation that the bilirubin in the serum of patients suffering from obstructive jaundice reacts at once with the diazotized sulphanilic acid to give a deep red colour, while the bilirubin in serum from patients with haemolytic jaundice gives the reaction slowly or not at all in untreated serum, but gives a fairly prompt response after treatment of the serum with alcohol and removal of the protein which is thereby precipitated. The colour obtained in the latter case is purple. With some serums an intermediate type of result is obtained—namely, the prompt development of a red colour which later becomes purple.

To interpret these results van den Bergh assumed that two forms of bilirubin exist—the one reacting directly with the sulphanilic acid reagent, and present typically in cases of obstructive jaundice, and the other reacting to an appreciable extent only in the presence of alcohol and after precipitation of protein, and present typically in cases of haemolytic jaundice. Intermediate types of result he assumed to be due to the presence of both forms.

On this assumption of two forms of bilirubin largely rests the modern theory of jaundice as described, for example, by McNee.¹ The actual difference between the two forms of bilirubin, which is responsible for their different behaviour has not yet been clearly demonstrated. It is considered by some that the presence of protein is responsible for the different behaviour of the two forms, the bilirubin of haemolytic jaundice being thought to be in combination with protein, while in obstructive jaundice it is in combination with an alkali. Others have attributed the different properties of the two forms to physical differences between them. It seems to us to be of considerable importance to ascertain if possible the actual mechanism underlying these different reactions, since such a knowledge must necessarily help in explaining the production of bile pigment in the body and the production of jaundice. It is with this object in view that the work about to be described has been undertaken.

It appears to us that the most important fact bearing on the problem is that bilirubin is an acid, having, according to the formula suggested by H. Fischer, two carboxyl groups. It is therefore capable of forming salts which