no necessity to place restriction on the movements of other occupants provided they are frequently examined and remain well. Those in contact with the case may be advised to use antiseptic nasal sprays, douches, and throat gargles. Any persons in the infected household who suffer from sore throat or other symptoms suggestive of an abortive attack should be medically treated and isolated until they have recovered. The sick-room should be thoroughly cleansed and disinfected at the end of the illness.

Although there is no specific treatment, much may be done to sustain and tide the patient over the acute period of attack. Confinement to bed, the services of a trained nurse, and treatment as an infectious disorder are primary essentials. In many cases transient or permanent relief with diminution of stupor follows on the withdrawal of cerebro-spinal fluid by lumbar puncture. It is seldom advisable to administer hypnotics, morphine, or other preparation of opium; urotropine, if prescribed, should be administered in small doses with caution and with suitable tests as a guide. Hall advises belladonna in the treatment of chronic forms of the disease.

CONCLUSION.

To encephalitis lethargica we may apply the words of Harvey: "Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by the careful investigation of cases of rarer forms of disease."

The study of encephalitis lethargica has made many problems in neurology and physiology plain; but the existence of this tragical disease in our midst is a heavy price to pay for the acquisition of new learning. Sir Thomas Browne wrote: "Some will allow no diseases to be new, others think that many old ones are ceased; and that such which are esteemed new will have but their time." But even if this last is true of encephalitis lethargica, it behoves us all to endeavour to shorten the time of visitation. You will have gathered from what has been said how serious is the disease and how deplorable and frequent are its after-manifestations.

Further study of the malady will add to our knowledge and will furnish us with fresh weapons for attack and defence. In this crusade the team work of the epidemiologist, the physician, and the pathologist is all-important.

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THE ABSORPTION OF MERCURIALS FROM OINTMENTS APPLIED TO THE SKIN.

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In two previous papers by one of us¹ an attempt was made to determine the relative values of the different substances used as bases for ointments, both as regards protection and absorption, and it was found that lard and hydrous wool-fat were absorbed more readily than the paraffin bases. We have no information as to whether the drugs combined with these bases to form ointments are absorbed *pari passu* with the base, or whether the bases readily part from the drugs so that the latter may be absorbed either more quickly or more slowly than the base; neither do we know whether a drug dissolved in the base behaves differently from one which is merely mechanically mixed with it. It seemed desirable, therefore, to attempt to determine these points by the method described in the previous papers, but work on these lines was interrupted for some years by the war, and has only recently been completed and the following results obtained with respect to certain mercurial ointments.

The mercurial ointments were selected for study for two reasons: first, because the absorption of mercury through the skin is of importance in regard to its clinical use—in some cases desirable, in others to be avoided; and secondly, because mercury and its compounds can be quantitatively estimated with great accuracy. It was found, however, that the accurate determination of mercury and its compounds when combined with fats or paraffins of various composition presented special problems in analysis and required special methods; these methods were first worked out and the results have already been published by one of us.²

The method employed was to make an accurate determination of the mercury in a sample of ointment; a carefully weighed quantity of this was then rubbed into a definite area of skin, about 20 square inches, for a definite time. The unabsorbed ointment was then scraped off the rubbing finger and the surface of the skin by a dulled Gillette safety razor blade fixed in a convenient handle, and again weighed. To avoid the necessity of wiping the instrument the scraper was weighed with the ointment both before and after rubbing. The amount of mercury in the unabsorbed ointment was then determined. The loss of weight represents the amount of ointment absorbed together with that lost by manipulation, and as the latter is fairly constant in dealing with preparations of similar consistence the results afford a relative indication of the respective amounts absorbed. From a comparison of the analysis of the ointment before rubbing with the analysis of the unabsorbed ointment it is easy to calculate the amount of mercury, or mercurial salt, absorbed as well as the amount of base.

It was found, after doing a number of preliminary experiments, that absorption was not so good when the skin was cold—as, for example, in the morning in cold weather. In order, therefore, to reduce the number of variable factors as much as possible the experiments were always carried out in the afternoon, and the skin area was well washed with hot soapy water and thoroughly dried immediately before rubbing. It was also found that the variable thickness and texture of the skin in different parts of the body and in different persons affected the amount absorbed, and the experiments from which any conclusions were drawn were all carried out on the same

person and on the flexor surface of the forearm from the wrist upwards, a surface free from hair and convenient to use. In order to verify the results obtained a number of the more important experiments were repeated independently after twelve months' interval, with substantially the same results. Over 130 experiments were done in all.

The following tables summarize the results obtained by this method, an average experiment being given in each case; for the sake of uniformity the amount of mercury or mercurial salt absorbed has been calculated as the weight in grams which would be absorbed from 100 grams of the original ointment. In the case of the mercury ointments this is estimated as metallic mercury, in the case of the oxide and oleate as mercuric oxide, in the case of calomel as HgCl_2 , in the case of ammoniated mercury HgNH_2Cl , and in the case of the salicylate as metallic mercury.

METALLIC MERCURY.

All ointments used were nominally of B.P. strength 30 per cent. The amount of mercury absorbed was found to vary with the size of the globules of mercury examined microscopically; the absorption from one sample of hand-made ointment with large globules was practically negligible, so all ointments were examined microscopically before they were used for experiment, and rejected unless the mercury was in a fine state of division and equally diffused through the fatty base.

Lard Base.—A comparison of experiments in which the duration of the rubbing was varied shows that at first the lard is absorbed more rapidly than the mercury, but on continued rubbing the mercury is absorbed more rapidly than the base. Thus the proportion of mercury in the unabsorbed ointment rises about 2 per cent. after a short rubbing, but only 0.88 per cent. after prolonged rubbing. The total absorption of the ointment with a lard base reached 22 per cent. in some cases; the average was 15.98 per cent.

Soft Paraffin Base.—The proportion of mercury in the unabsorbed ointment rose about 1.4 per cent., and then remained constant, showing that in the first instance the

Two Minutes' Rubbing.

Mercurial.	Base.	Melting Point of Base.	Total Loss.	Mercury in Original Ointment.	Mercury in Unabsorbed Ointment.	Mercury Absorbed from 100 grams of Original Ointment.
		Cent.	%	%	%	Grams.
Metallic mercury*	Benzoated lard	41°	15.5	31.20	33.2	3.15
Metallic mercury	Soft paraffin	40°	12.8	28.93	30.48	2.36
" "	Hydrous wool-fat	44°	20.0	30.34	35.3	2.10
Mercuric oxide	Benzoated lard	41°	8.50	8.85	9.24	0.40
" "	Benzoated lard	41°	8.46	18.96	19.05	1.52
" "	Benzoated lard	41°	9.74	30.85	31.47	2.45
" "	Soft paraffin	47°	7.76	9.45	9.72	0.49
" "	Hydrous wool-fat	44°	18.18	9.19	10.72	0.42
Mercuric oleate†	Oleic acid	15°	10.13	17.41	17.3	1.86
Calomel	Benzoated lard	41°	9.2	20.5	22.0	0.6
"	Soft paraffin	45°	8.15	20.5	21.85	0.4
"	Hydrous wool-fat 60% Soft paraffin 20%	44°	17.6	20.0	23.2	0.8
Ammoniated mercury	Benzoated lard	41°	11.0	5.5	5.8	0.4
"	Benzoated lard	41°	14.6	11.5	11.7	1.5
"	Soft paraffin	47°	8.5	4.6	4.9	0.1
"	Ung. paraff. (B.P.)		8.6	10.1	10.3	0.7
"	Hydrous wool-fat 40% Soft paraff. 50% (U.S.P. formula)		15.7	11.5	13.1	0.5
Mercuric salicylate	Benzoated lard	41°	10.3	10.0	10.5	0.6

* Ung. hydrarg. B.P.

† B.P.; nominal 20 per cent.

Ten Minutes' Rubbing.

Mercurial.	Base.	Melting Point of Base.	Total Loss.	Mercury in Original Ointment.	Mercury in Unabsorbed Ointment.	Mercury Absorbed from 100 grams of Original Ointment.
		Cent.	%	%	%	Grams.
Metallic mercury*	Benzoated lard	41°	18.9	31.2	32.6	4.76
Metallic mercury	Soft paraffin	40°	12.26	28.93	30.13	2.49
" "	Hydrous wool-fat	44°	28.19	30.34	38.42	2.75
" "	Hydrous wool-fat + lard and olive oil		19.74	32.37	35.82	3.62
Mercuric oxide	Benzoated lard	41°	14.03	8.85	8.84	1.25
" "	Benzoated lard	41°	11.34	18.96	18.99	2.12
" "	Benzoated lard	41°	14.94	30.85	30.92	4.55
" "	Benzoated lard	41°	16.54	37.14	37.95	5.17
" "	Soft paraffin	47°	12.08	9.45	9.86	0.78
" "	Hydrous wool-fat	44°	31.24	9.19	11.65	1.18
Mercuric oleate†	Oleic acid	15°	11.23	17.41	15.93	2.33
Mercuric oleate with 50% benzoated lard	Benzoated lard		9.77	8.18	7.74	1.2
Calomel	Benzoated lard	41°	13.5	20.5	22.5	1.0
"	Soft paraffin	45°	6.5	20.5	21.1	0.8
"	Soft paraffin 20% Hydrous wool-fat 60%		22.5	20.0	25.1	0.5
Ammoniated mercury	Benzoated lard	41°	14.5	5.5	5.7	0.6
"	Benzoated lard	41°	11.5	11.5	11.6	1.3
"	Soft paraffin	47°	8.1	4.6	4.6	0.4
"	Ung. paraff. (B.P. 1893)		8.1	10.1	10.2	0.7
"	Hydrous wool-fat 40% Soft paraffin 50% (U.S.P. formula)		15.3	11.5	12.5	0.9
Mercuric salicylate	Benzoated lard	41°	11.6	10.0	10.2	1.0

* Ung. hydrarg. B.P.

† B.P.; nominal 20 per cent.

paraffin is absorbed more rapidly than the mercury, but on continued rubbing they are absorbed at the same rate. It was found that the total absorption of paraffin ointments never rose above 12 to 13 per cent., the average being about 8 per cent. As the percentage of mercury in the unabsorbed ointment does not fall on continued rubbing it appears impossible for a high absorption of mercury to be obtained by using a paraffin base.

Hydrous Wool-fat.—Here the proportion of mercury in the unabsorbed ointment rises about 5 per cent. after two minutes' rubbing, and continues rising up to 8 per cent. after ten minutes' rubbing, showing that the wool-fat is absorbed much more rapidly than the mercury; this may partly be due to the water present. The highest absorption of mercury in the case of hydrous wool-fat was 2.75 after a very large total absorption of 28 per cent. This compares with an absorption of 6 of mercury with a total absorption of 22 per cent. in the case of the lard ointment, and the highest absorption of mercury from a paraffin ointment of 2.55 after a total absorption of 13 per cent. Hydrous wool-fat, therefore, appears to have no advantage over paraffin as a base for mercurial ointment, as the wool-fat is absorbed and the mercury left behind. Lard appears to be the best base, as it is the only one in which, after the preliminary high absorption of the base, the mercury tends to pass in more rapidly than the base. As hydrous wool-fat gives a high total absorption, while lard appears to act better in carrying the mercury through the skin, experimental bases containing a mixture of the two were tried. The percentage of mercury in the unabsorbed ointment continued to rise, showing that these bases were absorbed more rapidly than the mercury, and that the larger total absorption obtained by the addition of hydrous wool-fat has no advantage over the lower total absorption of the lard alone.

MERCURIC OXIDE.

Ointments were made containing yellow mercuric oxide:

- (a) 10 per cent. in soft paraffin.
- (b) 10 per cent. in 10 per cent. soft paraffin and 80 per cent. hydrous wool-fat.
- (c) 10 per cent. in benzoated lard.
- (d) 20 per cent. in benzoated lard.
- (e) 30 per cent. in benzoated lard.
- (f) 40 per cent. in benzoated lard.

With the lard base there is, after a short rubbing, a slight rise in the percentage of mercury in the unabsorbed ointment, but not so marked as in the case of the mercurial ointment, and with longer rubbing this falls to the original percentage and remains constant, showing that the mercury and the base are absorbed at the same rate; the highest amount with the 10 per cent. ointment was 1.25 of mercury. The amount of mercury absorbed increased with the strength of the ointment; the 20 per cent. ointment gave approximately twice as much mercury absorbed as the 10 per cent., and the 30 per cent. three times as much with the same base. The 40 per cent. gave rather more than the 30 per cent., but not in proportion; this appears to be about the limit for maximum absorption.

With the paraffin base the percentage of mercury in the unabsorbed ointment remained fairly constant and almost the same as in the original ointment, so that the mercury and the base are absorbed practically at the same rate. The highest absorption from the 10 per cent. ointment with the paraffin base was 0.89.

With the hydrous wool-fat base, as in the case of mercury ointment, the percentage of mercury in the unabsorbed ointment continues to rise with prolonged rubbing, showing that the base is absorbed more quickly than the mercury, which is left on the surface of the skin. The highest absorption obtained from the 10 per cent. ointment in hydrous wool-fat was 1.18.

A comparison of the results obtained from the 30 per cent. mercuric oxide with those from mercury ointment of equal strength shows that the mercuric oxide is absorbed more rapidly than the metallic mercury in proportion to the total absorption.

MERCURIC OLEATE.

The B.P. preparation nominally contains 20 per cent. of mercuric oxide combined with oleic acid; a sample prepared according to the B.P. directions was found to contain 17.41 per cent. of mercuric oxide, and formed a sticky and adhesive product not easy to rub into the skin. The percentage of mercury in the unabsorbed oleate showed no change, so that the mercury and the base were absorbed at the same rate, probably without any decomposition of the oleate. The total absorption did not rise very high, and as the rubbing of it was not very satisfactory an ointment was prepared which contained 50 per cent. of the mercuric oleate and 50 per cent. of benzoated lard; the percentage of mercury in this was found to be 8.18. After ten minutes' rubbing the percentage of mercury in the unabsorbed ointment was reduced, showing that the oleate was absorbed more rapidly than the lard. On the whole it was found that mercury was absorbed more rapidly from the oleate than from mercuric oxide or metallic mercury ointments of equal strength.

CALOMEL.

The B.P. ointment of 20 per cent. mercurous chloride in benzoated lard was used and compared with 20 per cent. of the mercurous chloride in soft paraffin and 20 per cent. in a mixture of 20 per cent. soft paraffin and 60 per cent. of hydrous wool-fat. In the case of the lard base the proportion of calomel in the unabsorbed ointment rose about 2 per cent. and then remained constant, so that the calomel appeared to be absorbed less readily than any of the mercurials previously considered. The highest figure obtained was 1.2, which is low for a 20 per cent. ointment. With a paraffin base the highest figure obtained was 0.8, and the same figure with the paraffin and hydrous wool-fat base. In the latter case the proportion of calomel in the unabsorbed ointment rose from 20 per cent. in the original ointment to 25.8 per cent., showing the rapid absorption of the hydrous wool-fat, leaving the calomel behind. In

the case of the paraffin base the rise in the percentage of calomel in the unabsorbed ointment was much less (under 1 per cent.) and remained constant.

The results obtained were not in accord with the experiments on rabbits of Schamberg, Kolmer, and Raizios,³ who state that calomel ointments are as well absorbed through the skin in rabbits as the ordinary blue ointment, if not better.

AMMONIATED MERCURY.

The following ointments were prepared and estimated as to content of mercuric ammonium chloride:

- Ammoniated mercury 5% in benzoated lard (B.P. 1914).
- Ammoniated mercury 10% in benzoated lard.
- Ammoniated mercury 5% in soft paraffin.
- Ammoniated mercury 10% in paraffin ointment (B.P. 1898).
- Ammoniated mercury 10% in 40% hydrous wool-fat and 50% soft paraffin (U.S.P. formula).

The amount of absorption with the 10 per cent. ointments was about twice as great as with the 5 per cent. ointments. With the lard and paraffin bases the percentage of mercurial in the unabsorbed ointment showed little change; the base and the mercury were absorbed at practically the same rate—there was no initial rise as in the case of metallic mercury and calomel; ammoniated mercury, therefore, showed a rate of absorption similar to mercuric oxide. With the hydrous wool-fat base the proportion of mercury in the unabsorbed ointment was raised by 1 to 2 per cent., showing that the hydrous wool-fat had been absorbed more quickly than the mercury; this effect was also noted in the fact that the mercury was more easily extracted from the unabsorbed ointment owing to the smaller amount of hydrous wool-fat left in it. The maximum of absorption with the hydrous wool-fat base was 1.

MERCURIC SALICYLATE.

It was thought desirable to compare some organic salt of mercury with the inorganic preparations, and for this purpose the salicylate was chosen, because it is a stable compound, insoluble in water, forms a fine amorphous powder, and is official in the U.S.P.

A 20 per cent. ointment was prepared with benzoated lard, and the results were very similar to those obtained with the yellow oxide and the ammoniated mercury ointments of the same strength. There was a slight rise in the percentage of mercury in the unabsorbed ointment, and the maximum absorbed was 1.5.

MECHANISM OF ABSORPTION.

While we are ignorant as to the exact mode in which absorption through the skin occurs, whether through the epidermis, the sebaceous glands, or the sweat glands, a study of the experiments already carried out does afford some facts which have a bearing upon this problem.

It is evident that the absorption of the medicament depends upon the following factors when the same area of skin is used for the experiments: (a) nature of the base; (b) nature of the medicament; (c) strength of the medicament.

As regards absorption of the base itself the results are entirely in agreement with those previously published by one of us in the papers already referred to—namely, that hydrous wool-fat is absorbed most rapidly, provided the proper amount of water is present, which is rarely the case unless the ointment is freshly made; lard is absorbed almost as well—15 per cent. as compared with 20 per cent.—and soft paraffin considerably less, the time of rubbing being the same in each case. These differences may partly depend upon physical characters. In connexion with this factor the appearance on rubbing is important; on the skin lard becomes liquid and scrapes off still in a liquid condition; soft paraffin only becomes semi-liquid, and scrapes off stiff at about its original consistence; hydrous wool-fat is quite firm when scraped off the skin. The melting point of soft paraffin is not so much higher than that of lard as to account for this difference; possibly a difference in viscosity may be a factor. That the liquid character of the lard is not the only factor in the absorption is shown by the high absorption of the hydrous wool-fat which remains firm on the skin.

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.

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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