method of chloroform anaesthesia has not been applied to diphtheria, in spite of the suggestive experiments of Billard in this connexion. Since February, 1930, we have tried the method in six cases, four without any success. We must frankly admit, however, that the treatment was applied only when the patients were *in extremis*, so that no really satisfactory conclusions can be drawn from these cases.

It is absolutely necessary to intervene early if the method is to be applied at all. As soon as nervous complications begin to appear chloroform anaesthesia should be at once combined with the administration of large doses of anti-diphtheritic serum, following the same technique as for tetanus, and giving the serum subcutaneously, intramuscularly, or even, in the hypertoxic cases, intravenously. The intraspinal route might also be employed, although this, to our knowledge, has not yet been tried in diphtheria. Such are the general indications which we advise, and which we shall ourselves follow in the future.

Encephalomyelitis and Poliomyelitis.—The phylactic method of chloroform anaesthesia might, by analogy, be used in encephalitis and poliomyelitis, but it would be necessary to have at our disposal corresponding specific serums. As far as poliomyelitis is concerned, Petit's anti-poliomyelitis serum might well be employed in this way, and may possibly give far better results than those obtained hitherto.

Against encephalomyelitis there is, as yet, no specific serum, but it is interesting to note that urotropine, which was quickly found to have a favourable therapeutic effect in this condition, probably acts in the same phylactic way as chloroform. Urotropine becomes decomposed in the tissues and gives rise to formaldehyde, which displaces the toxins from the nerve centres and becomes fixed to the lipoids of the cells. Billard's experiments with urotropine suggest this conclusion. As with chloroform, similar results were obtained; if urotropine is injected into a guinea-pig some fifteen minutes after the administration of a toxin (tetanus anatoxin), the animal dies more rapidly. But toxins differ among themselves, and it is possible that if the toxins of encephalitis were liberated in the blood stream, the body would be better able to deal with them than when they are fixed in the central nervous system.

Other Indications.—Although so far we have only discussed the more common neurotropic diseases, it is evident that the phylactic method might quite well be applied to other infections having a particular affinity for the nervous system. Among these are certain cases of influenza, typhoid fever, herpes zoster, varicella,⁶ typhus, sleeping sickness, and of poisoning by strychnine, phalline, snake bite, the botulinus bacillus, curare, etc.

CONCLUSIONS

For purposes of simplification we have confined our attention to the use of chloroform alone as a phylactic agent, though, as we have seen, urotropine may act in the same way. We must add, however, that Billard, in experiments of the highest ingenuity, has shown that sparteine sulphate, gardenal, and especially certain mineral waters, possess the power of similarly protecting the nerve centres. Further research may discover yet other phylactic substances. Although Billard considered his discovery of phylaxis to be of theoretical interest only, it has nevertheless been shown by later workers to have practical implications of the highest order, and to offer therapeutic possibilities of the greatest value.

This short memoir, which Professor Achard⁷ read for the first time at the Académie de Médecine of Paris, is written solely with a view to giving an indication of the results that can be achieved by phylaxis, of showing that we have now in our hands a method of wide application,

capable in the future of leading to considerable advances in the treatment of the neurotropic diseases.

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DIAGNOSIS OF DRUNKENNESS FROM THE EXCRETION OF ALCOHOL

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As part of a more extensive study we have carried out a number of experiments on the excretion of alcohol by human subjects. In all these experiments the excretion both by the lungs and by the kidneys was measured, and the condition of the subjects with respect to intoxication was observed by various psychological tests and by the routine methods of examination used by police surgeons. It seemed to us desirable, in view of the fact that estimation of alcohol in the breath¹ and urine² has been recommended as a test of drunkenness, that our experiments should be separately reported, especially as they do not support the use of this method of diagnosis.

The subjects of our experiments were all young, healthy men, and were all light or moderate drinkers. The experiments all commenced at about the same time, three hours after a light lunch. Except in one or two cases when gin was used, the alcohol was given in the form of whisky, the same brand being used throughout, and was diluted with an equal volume of soda-water. Drinking-water or soda-water was allowed during the experiment. Samples of air and urine were collected before the alcohol was ingested and periodically afterwards. Psychological and routine tests were made at regular intervals, the examination, in a number of experiments, being carried out by a police surgeon, Dr. Cameron, to whom our thanks are due.

For the estimation of alcohol in the expired air, the subjects blew air through a solution of potassium bichromate and sulphuric acid, the delivery tube being terminated by a disk of Jena sinter glass in order to ensure the formation of small bubbles, and consequently the complete absorption of alcohol. The air then passed through a flow meter placed with a dial facing the subject, who was instructed to stop when the required volume of air—usually five litres—had passed through. Control experiments with air saturated with alcohol vapour showed that at the rate of blowing adopted the alcohol was completely absorbed. The amount of alcohol absorbed and oxidized by the bichromate was determined, as usual, by the addition of potassium iodide in excess and titration with sodium thiosulphate. The quantities and concentrations of the solutions used were those recommended by Southgate³ for the estimation of alcohol in urine. The analysis of the urine was carried out by the method and with the apparatus described by Southgate.

In the air analysis a fallacy may be introduced by the difficulty of obtaining strictly comparable samples. If the expiration is complete, the air analysed will include a larger amount of alveolar air, with a relatively high alcohol content, than if the breathing is shallow. Control of the breathing throughout the experiments is difficult,

Mg. Alcohol per
Litre Air

FIG. 1.—The effect on the excretion of alcohol by the lung of altering the depth of breathing.

RELATION BETWEEN THE ALCOHOL CONCENTRATION OF THE BREATH AND THAT OF THE URINE

According to Bogen¹ analysis of the expired air offers a convenient means of ascertaining the alcoholic concentration of the blood, since the quantity of alcohol in the expired air bears a definite relationship to that in the urine and therefore to the amount in the blood. Our results entirely fail to confirm this statement. The curve showing

Mg. Alcohol per
Litre Air

FIG. 2.—The excretion of alcohol by the lung.

the course of excretion through the lung is of the same general shape as that for kidney excretion (Fig. 2), but the maximum concentration in the breath is usually reached much earlier than it is in the urine. In Fig. 2 we have plotted a series of curves showing the alcohol concentration in the breath of a number of individuals after ingestion of 216 c.cm. of whisky, and Fig. 4 shows the alcohol concentration in the urine in the same and other experiments. Examination of these curves shows that there is no constant ratio between the concentration of alcohol in the breath and in the urine. Thus forty

minutes after the ingestion of the alcohol, C_1 is excreting three times as much by the lung as is G . (not charted), but only twice as much by the kidney; after ninety minutes the relative amounts in the breath remain approximately the same, while in the urine G is excreting slightly more than C_1 .

In the experiment with W. W., the ratio between the concentration of alcohol in the breath (per litre) and that in the urine (per c.cm.) is 0.34, 0.31, 0.31, and 0.41 in the different pairs of samples; in that with G. S. the ratio is 3.4, 0.36, 0.25, 0.27, and 0.32; and in that with C_2 it is 2.25, 0.65, 0.34, and 0.26. Even if the first ratio in each series be excluded, these figures show too great a variation to justify the claim of a quantitative relationship between the concentrations of alcohol in the breath and urine.

EXCRETION OF ALCOHOL BY THE KIDNEY

It has repeatedly been stated that there exists a definite relationship between the alcohol concentration of the blood and that of the urine. Thus Southgate and Carter² give the ratio as 1 to 1.35, and other workers have obtained similar though not identical figures. It seems to us, however, that in calculating these ratios, insufficient attention has been paid to the fact that whereas a sample of blood shows the concentration of alcohol in the blood at the moment of withdrawal of the sample, a sample of urine shows merely the average concentration of alcohol in the kidney secretion during a period of time. Hence it appears that the exact ratio found experimentally will depend on the frequency with which urine samples are collected and compared with the blood. Thus if, as seems possible,* the true ratio is unity, and the concentration of alcohol in the blood at a given moment is equal to the concentration in the urine secreted at that moment, it is to be expected, samples of both fluids being collected at the same time, that:

1. If urine is collected at the end of a period during which alcohol is being absorbed and the blood concentration is increasing, the concentration of alcohol in the urine will be less than that in the blood.
2. If the time during which the urine sample has been secreted covers the peak of alcohol absorption, the concentration of alcohol in the two fluids will be approximately equal.
3. If the urine sample covers a period during which the concentration of alcohol in the blood has been falling, the concentration of alcohol in the urine will be greater than that in the blood. The shorter the periods during which urine is allowed to collect in the bladder, the closer will be the approximation of the curves of blood and urine alcohol concentration.

A second result which is to some extent dependent on the same factor—the time interval between the successive samples of urine—is the shape of the urine alcohol concentration curve. This is true, in fact, not only of urine, but also of blood. The longer the interval between samples, the smoother will be the curve, a fact which is illustrated in Fig. 3. Here the curve with black dots is obtained by plotting the results of half-hourly samples of urine. The curve with circles is obtained from the same experiment, by combining pairs of analyses to give the concentration of alcohol in hourly samples. If the rate of excretion of alcohol by the kidney is a true reflection of the concentration of alcohol in the blood, a curve of the black dotted type is more probable than one of the shape found by Mellanby⁴ and by Southgate and Carter.² The curves given by these authors indicate a constant rate of disappearance of alcohol from the blood, and therefore, since the actual

* This supposition, which implies a simple filtration of alcohol through the kidney, is supported by the fact that, while the concentration of alcohol in the urine follows a regular curve, the amount does not. In other words, the concentration does not depend on the volume of urine passed. Experiments of our own, on animals, indicate that, with urine collected over very short periods, the ratio between blood and urine alcohol concentrations is approximately unity.

amount excreted by the kidney is negligible, a constant rate of oxidation of alcohol, no matter what the concentration in the blood. Now this is contrary to experience with other types of foodstuff, and even in the case of alcohol it is not supported by any evidence save the shape

FIG. 3.—The influence of the interval between successive samples of urine on the shape of the kidney excretion curve.

of the urine excretion and blood concentration curves as found by Mellanby. The metabolism experiments carried out by him show that alcohol can be metabolized at the average rate of 10 c.cm. per hour, not that it is metabolized at that rate in all circumstances. The excretion curves we have obtained from samples of urine collected at short intervals fit in with this view, for, though they indicate that the rate of oxidation of alcohol is to some extent dependent on the concentration in the blood, they show that the time required for the complete removal of alcohol from the body is roughly proportional to the amount ingested.

MEDICO-LEGAL VALUE OF DETERMINATIONS OF ALCOHOL IN THE URINE AND BREATH

Except as showing that the suspected person has or has not consumed alcohol within a short time of the test, estimation of alcohol in the breath appears to be valueless. Since, as we have shown, there exists no constant relationship between the amount of alcohol in the breath and that in the urine (or, therefore, that in the blood) it is not possible to draw, from analyses of the breath, valid conclusions as to the amount of alcohol consumed. As to the diagnosis of drunkenness, the arguments set out below apply to expired air as well as to urine.

So far as the urine is concerned, determination of the alcohol content can be of value in the diagnosis of drunkenness if:

1. The concentration of alcohol in the urine bears a constant relationship to the concentration in the blood.
2. The concentration in the blood bears a constant relationship to the concentration in the tissues.
3. The concentration in the blood and tissues is an index of the degree of intoxication.

Leaving aside for the moment the question of the degree of intoxication, it does seem that the first two factors are satisfied sufficiently closely to allow of urine analysis giving an idea of the minimum amount of alcohol consumed. For it appears that, at the moment of secretion, urine contains about the same concentration of alcohol as the blood, though in actual practice the relation

departs somewhat from this simple one, since the urine actually obtained is secreted over a period of time during which the concentration of alcohol in the blood is changing. There is also evidence that the tissues at any given moment contain approximately the same concentration of alcohol as the blood, the term "tissues" being taken as including all the large organs and the skeletal muscle, but not the bones and fat deposits, which are almost alcohol-free. Thus from the blood concentration—and less exactly from the urine concentration of alcohol—it is possible to calculate the approximate total amount of alcohol in the body at any given time, and therefore the minimum amount consumed. In this calculation, allowance must be made for the weight of the skeleton and adipose tissue, which together normally account for about a third of the total body weight. Hence the minimum amount of alcohol taken is equal to (about) $\frac{2}{3} \times \text{body weight} \times \text{percentage of alcohol in blood}$. Closer approximation can be made if one knows the time that has elapsed since the ingestion of alcohol, since that allowance can be made for the amount metabolized. The crudity of the calculation, however, renders such refinements dangerous.

The amount of alcohol calculated from the blood concentration is strictly a minimum, but inspection of certain of our experimental results shows the danger of attempting to go further and to calculate the actual amount consumed. The variation in the rate of excretion, in the time between ingestion and maximal blood concentration, and the possible variation in the rate of metabolism, not only among different individuals, but in the same individual on different occasions, all tend to make such extrapolations unsafe. A study of our curves shows very

FIG. 4.—The excretion of alcohol by the kidney in different individuals who have taken the same dose.

clearly that this danger is not imaginary, and that the differences in the alcohol concentration of the urine found in different experiments with the same consumption of alcohol in similar circumstances cannot be correlated either with body weights or with the habits of the subjects in regard to the drinking of alcoholic liquors. Thus in Fig. 4, G. S., who is practically teetotal and weighs 12 st.,

and W. W., who is a moderate drinker and weighs 10 st., both produce urine with, throughout the experiment, a lower concentration of alcohol than that of C₂, who is not in the habit of taking alcohol regularly, and who weighs 12 st. In these cases, however, as in all others we have studied, the calculation of the minimum amount that can have been taken from any single specimen of urine gives a result less than the amount actually taken. Hence such a calculation allows one to make a perfectly safe deduction as to the minimum amount of alcohol taken, but not of the actual amount.

DIAGNOSIS OF ALCOHOLIC INTOXICATION

As to the diagnosis of alcoholic intoxication, our results do not support the idea that estimation of the concentration of alcohol in either breath or urine is a valuable aid in diagnosis. Obviously, with very high concentrations such as 0.4 to 0.5 per cent. there is no doubt as to the diagnosis, but in these cases the circumstances are such that even without the analysis of urine there is no difficulty. Carter takes 0.2 per cent. as the dividing line above which a diagnosis of drunkenness is justified, and similar standards are set up by others, but to us this appears a very dangerous procedure. We have met a case of undoubted drunkenness—a semi-comatose condition—in which the concentration of alcohol in the urine never reached this level, and that in an almost teetotal subject who drank 250 c.cm. of whisky. Though this does not constitute a serious indictment of the validity of the

method of diagnosis, since it is only claimed that a man showing over 0.2 per cent. of alcohol in the urine is drunk, and not that one showing less than this is sober, other of our results do invalidate the test. For in certain of our experiments the subjects were classed as sober by the police surgeon and showed no evidence of being affected by alcohol when tested by psychological methods, but were nevertheless excreting urine containing more than 0.2 per cent. of alcohol. Hence, with a urinary alcohol concentration of about this figure, the diagnosis is extremely doubtful; and yet it is just here, near the borderline between drunkenness and sobriety, that the test would be most useful. We are forced to the conclusion, therefore, that as a means of diagnosis of drunkenness urine analysis is valueless, though as a means of determining the minimum amount of alcohol consumed, it may on occasion prove useful.

It is a pleasure to express our thanks to Dr. Drever, who devised and helped us with the psychological tests used in our experiments; to Dr. Cameron, who applied to our subjects the tests used in police station examinations; and to the subjects who volunteered to undergo what were often unpleasant experiences. One of us (C. P. S.) is indebted to the Medical Research Council for a part-time grant.

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EAR COMPLICATIONS OF INFLUENZA *

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During December, 1930, and the first three months of last year a group of acute ear cases associated with influenza came under my care, and the complications arising from them interested me so much that I decided to put them on record. The following are abbreviated notes, not of all cases seen in the period mentioned, but of eleven cases of typical influenzal ear infections. All are of a recent date except two, one of which shows the interesting sequel of chronic labyrinthine changes following an attack of acute middle-ear suppuration nine years previously; the other is that of a simple mastoid and lateral sinus operation, which was soundly healed for two years, with nearly full hearing, and was followed this year by a fresh middle-ear infection and large abscess formation in the mastoid.

CASE I

A woman with middle- and internal-ear deafness was seen because of deafness in the left ear. She had had a sharp attack of influenza, with moderate pyrexia, one month before. Pain in the left ear set in after two days, followed by a "serous discharge" (doctor's words) for three days. At this time headache and giddiness were noticed. Examination revealed that the membrane was intact and clean. No spontaneous nystagmus or Rombergism present. Low notes heard well (except Fork 16 D.V.). High notes much shortened; also bone conduction. Whisper heard 1½ feet away. This improved to 7 feet after inflation.

Three months later doctor reported that patient's hearing had improved.

CASE II

Woman, aged 32, was seen nine years ago for acute middle-ear suppuration; recently for Ménière's syndrome.

January 27th, 1922.—Influenza three weeks previously. Temperature over 100° F. for a few days. Right ear-ache

eighteen days before. Bled first, then watery; thick discharge ever since. Pain every day or night for a fortnight. Discharge free at night. The membrane was injected and mastoid tip tender on pressure. Treated with 5 per cent. glycerin acid carbolic, and condition cleared up in three weeks.

May 5th, 1931.—History of giddy attacks and sickness for one year. More frequent the last six months. The tympanic membrane not damaged. Hearing in right ear was very poor. All forks below 512 D.V. not heard by air. High forks much shortened. Bone conduction poor. Romberg slight. Nystagmus indicated an irritative lesion in right ear.

CASE III

Man, aged 32, had influenza and pyrexia for a few days a month before. Felt giddy, and went deaf in the right ear. Giddiness passed off in two days, but deafness persisted. Tympanic membrane looked normal. No hearing could be elicited in the right ear, if left excluded. No Romberg or nystagmus.

CASE IV

Man, aged 35, had pain for two days in left ear. Temperature 102° F. Treated with carbolic drops (2 per cent.). On April 8th, 1931, strength increased to 10 per cent., and injection of S.U.P. given. Discharge began next day, and cleared up in twelve to fourteen days. Two months later membrane and hearing normal.

CASE V

Woman, aged 28, with middle-ear inflammation, suppuration, mastoiditis, and perilyabyrinthitis. Seven weeks before she had influenza and pyrexia for a week. Ten days later pain in right ear, followed by discharge in twenty-four hours. This continued. Two weeks later paracentesis, and removal of granulation by curette (another surgeon). On February 25th, 1931, there had been giddiness, nausea, and vomiting for three days. Pain, stiffness in neck muscles, pain in right temporal region; temperature 101° F. Only slight tenderness over mastoid. More tender over the root of zygoma. Free aural discharge; Romberg slight; nystagmus to right; membrane red and swollen, with a small nipple-like projection from attic region. As the mastoid symptoms and signs appeared to be less urgent than the labyrinthine disturbance no immediate operation was done for fear of increasing the latter and setting up labyrinthitis and its sequels.

Patient was kept in bed, S.U.P. being used the first three days. Aural discharge continued twelve days later. When

* Paper read to the Section of Laryngology at the Annual Meeting of the British Medical Association, Eastbourne, 1931.