of causing prolonged narcosis; we should kill the patient. More damage is done by ether; it is a different type of narcotic. This effect is not just specific to brain; it works with other organs, especially the liver. And here, again, the main effect is in respect of the carbohydrate. At narcotic concentrations these substances affect the metabolism of sugar. It was the appreciation of this fact, in the early days, which led us to seek for, and to find in our cases of prolonged narcosis evidences of ketosis. It was found that in most cases of prolonged narcosis symptoms develop which might be due to ketosis.

It was those facts which led us to consider modifying the treatment by glucose and insulin, and we published a paper showing that glucose and insulin administration had a favourable effect. Glucose and insulin are favourable because they combat the toxic effects of narcotics in organs in which the carbohydrate metabolism greatly depends on the glycogen-glucose metabolism. In the brain there is no glycogen metabolism; the brain works, because it must work, on glucose supplied by the blood. Insulin cannot effect narcosis in the brain, because insulin has its effects chiefly on the glycogen breakdown; it is more or less independent of the nervous system, so insulin cannot affect the narcosis treatment. But it can combat the effects of the narcotics on other organs than the brain.

Pathology.

The Phylactic Theory in the Treatment of Neurotropic Diseases.

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The conception underlying the phenomenon of "phylaxis", or protection of the nervous system, in neurotropic diseases was first enunciated by Billard (1931), late Professor of Physiology at Clermont-Ferrand. It was he who gave an explanation of the value of chloroform anæsthesia in tetanus. In regard to this matter, Billard wrote as follows:

> "Profoundly convinced of the essential importance of lipoids in the production of phylactic phenomenon, I wondered whether anæsthetics generally, which had already been shown by Nicloux to have an affinity for the central nervous system, and in particular, whether chloroform, which had enabled Overton to establish the existence of lipoids, did not have the power of so modifying lipoid equilibrium *in vivo* as to render animals either more sensitive or more refractory to neurotoxins."

Whether or not the role of the lipoids will ultimately be found to be as vitally important as stated remains to be seen. The essential point, however, is that experimental evidence strongly suggests that protection is afforded by chloroform against a lethal dose of tetanus toxin.

Billard was able to demonstrate the following results on guinea-pigs:

> 1. The injection into a guinea-pig of a lethal dose of toxin produced no reaction if the animal had been anæsthetized for about 3 minutes, 12–15 minutes before the injection, the animal, according to Billard, having been rendered refractory to tetanus toxin.
>
> 2. If the lethal dose of toxin is given some 10–15 minutes before the chloroform anæsthesia, the animal dies more rapidly than by injection alone. The virulence of the toxin is apparently increased. (The reason possibly being that the toxin, free and freed, becomes widely distributed

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by the chloroform, for which it may have some affinity, and the ready reversibility of the lipoid-chloroform combination leaves the toxin more extensively fixed in the central nervous system.)

3. If, in the second example, an injection of anti-tetanic serum is given either just before or just after the chloroform anæsthesia, the amount of serum used being 0·5 c.c. per 100 grm. weight, the animal survives, the action of the anti-serum neutralizing the action of tetanus toxin.

René Cruchet, Professor of Clinical Medicine at Bordeaux, from whose article these experiments have been quoted (*Brit. Med. Journ.*, January 16, 1931, p. 86), suggests that similar conclusions might be drawn with regard to other toxins which have a special affinity for the nervous system, and particularly to diphtheria. Under similar experimental conditions, identical results were obtained in cases of poisoning by sparteine and viper venene.

The phylactic property of chloroform, as would be expected, has not the same force when neurotropic toxins are already fixed in the nerve centres, but, because of its affinity for lipoids, it has the power to displace toxins already fixed in the nerve-cells, and therefore exerts a perhaps reduced but nevertheless protective action. This capacity of chloroform and also chloral hydrate is seen in the application of these substances to well-established cases of tetanus. Cruchet, in 1915, and Dufour, in 1925, have seen that, if anti-tetanic serum was given under chloroform anæsthesia, usually good results were obtained. The former also treated 5 children, of whom 3 made good recoveries; in the other 2 cases life was prolonged, the contractures, pain and trismus ceased and they died free from intense suffering. The failure in some cases is explained as being due to the liberation of nerve-fixed toxin into a system already incapable of further resistance, and the importance is stressed of giving enough antitoxin simultaneously with the anti-serum, as well as the necessity of giving the combined treatment early in he course of the disease.

Reference is also made to the possible use of the phylactic method in certain cases of influenza, typhoid fever, herpes zoster, sleeping-sickness, snake-bite and other neurotropic affections. Interestingly enough, only one reference is made to the barbiturates (gardenal), but Billard, in his experiments, has shown that urotropine, sparteine sulphate and especially certain mineral waters, in addition to gardenal, possess a similar power of protecting the nervous system. In gardenal we have the direct link between chloroform anæsthesia and the long list of barbiturate compounds, of which somnifaine is of more immediate interest. Even prior to this century, and as early as 1882, Gessinger sought to allay the excitement and restlessness of his psychotic patients by prolonged ether and alcohol narcosis, and one wonders what theories were then in vogue. In an attempt to justify the application of the phylactic theory to mental disorders, it is fortunate that at least some of our carefully formulated diagnostic labels are widely recognized as being organic in the special sense of toxæmias. It is therefore necessary to begin from this point, where at least there would seem to be reasonably safe grounds for assuming some exogenous cause, bacterial or otherwise. In my opinion the confusional insanities have, curiously enough, been almost neglected in regard to our subject, perhaps because they usually run their comparatively short course, the recovery-rate is deemed good, and further, such cases present greater risks to prolonged narcosis. Naturally, therefore, it is upon our failures in therapy that our attention has been focused. Of the fairly large number of types of insanity that have been subjected to prolonged narcosis, it would seem that the acute forms, such as mania and the manic phase of the cyclic psychosis, are the most successful. I submit that this fact is relevant to the views to be expressed. I cannot but regard mania and the manic phase of the manic-depressive groups as precisely similar, and that to cut short the pathological processes that may otherwise subsequently result in profound exhaustion, of which depression is in part symptomatic, is to avoid or minimize the vicious circle. The fact that

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somatic processes are involved in the toxæmia and participate in the general acceleration of vital activity seen in the manic state must in part contribute to the higher percentage of successes on the grounds that leucocyte defence, elimination and neutralization of toxins are also implicated, these being essential factors in recovery. In contrast to the foregoing we have schizophrenia, in which, for the sake of argument, I submit that we view the symptomatic end-point of a gradual and insidious neuro-intoxication, a drawn-out pathological process from childhood. I want to make it clear that it is necessary to make this assumption in order merely to draw attention by analogy to the scientific facts of phylaxis. The patient suffering from tetanus and *in extremis* with superadded sepsis does not respond to the anæsthetic or narcotic, his nervous system and somatic functions both being at a low ebb. Might this not be the case in many schizophrenics—a group that show only a limited response to somnifaine? Another aspect of the subject requires brief mention, being one which is closely bound up with phylaxis and its possible effects on the psychoses, positive and negative. What explanation other than a psycho-dynamic one can be given for the strong tendency to relapse even when complete mental normality has been obtained immediately following the narcosis? As a bacteriologist, I am tempted to believe that here we have an indication in many of our patients that there is, as the source of the intoxication, a pathogenic living agent, and therefore it is clearly one thing to remove toxins fixed in a susceptible nervous system, and quite another to eradicate from an extensive focus, such as the colon, organisms producing neurotoxins. Let me take this point a little further. In mania we would generally seem to have an acute sudden infective toxæmia. Deep narcosis, if given at once, acts mainly in the true phylactic sense. Such protection cuts into morbid neuro-somatic interactions, and a usually short-lived toxæmia terminates even more rapidly with the neurons and endocrines practically unimpaired, and prolongation of the illness through damage to the central nervous system is minimized. In the manic-depressive cycle it is worth considering that, in the latter phase, where the narcosis is less likely to be effective, the toxin has become localized in the nervous system, somatic response or reaction being therefore minimal—a state, in fact, of anergy to the infection. To liberate nerve-fixed toxins in this state is hardly likely to produce more than temporary improvement. What neuro-somatic responses initiate the manic phase are still obscure, but I venture to submit that there arises a condition of somatic allergy to the neuro-toxin in the sense that the blood proteins are first involved—a phase which rapidly extends its sphere of action to the sympathetic functions of the autonomic. The sympatheticotonia manifest by manics would seem to be in harmony with this view. The endocrine triad, controlled by the sympathetic and on which our defences depend, is stimulated, and the relatively increased leucocyte activity excites a reactive auto-intoxication from the foci of infection. This wave of intoxication, if not neutralized, will cause further damage to the neurons, which will either continue to accelerate their activity, or gradually neutralize this effect until exhaustion of the whole complex process intervenes. The effect of a phylactic agent operating in the early stages can better be appreciated on the above hypothesis, since the sooner it is applied the stronger are the somatic defence mechanisms once the autonomic is stimulated, and the less is the damaging effect on the neurons of metabolic and neurotropic toxins. In many patients the spontaneous recovery phase in manic-depressive cases should be capable of prolongation, and, if each manic phase were smothered at the critical moment, permanent stability might be obtained.

In the large proportion of the schizophrenic group, we would seem to have a state of more or less persistent anergy to bacterial infection, with greater localization of nerve toxin within the central nervous system—two factors working in harmony to produce in the main a picture of quiescent chronicity. Phylaxis, in such patients, seems doomed to give poor results, as indeed would appear to be the case. In formulating this hypothesis within the compass of a brief paper, other links have unavoidably had to be omitted, but in the main I believe the views expressed

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will stand closer examination, and at least might form a basis of researches designed to clarify a theory that is still obscure in many of its aspects.

The literature on the subject of prolonged narcosis shows a great diversity of ideas in explanation of why good if not brilliant results may be obtained, and similarly so for the failures, and on the latter subject there is considerable reticence. The psycho-dynamic theory, enlarged by Pulmer and Payne and many others, based on a psychogenesis, holds the field, whereas the physiogenic aspect is discarded as untenable by most workers in this field of therapeutics. This blind spot in our reasoning is reflected by an interesting lack of enterprise in collateral or adjuvant physiotherapy, except for one series of cases in the literature where T.A.B. protein shock was also given. The effects on the patients' physical state were often drastic if not dangerous, but the group of cases thus dealt with were significant, I maintain, in the recovery percentage. Here the mechanism of phylaxis operating in mental illness, as now put forward, would seem to find a place, if the implications of somatic activity and reactivity are correlated with neuronic protection and elimination of toxins. It seems to me that it is time we appreciated more clearly that, to induce a narcosis, even by the safest possible means, we can only be dealing with one phase of a morbid process. The phylactic theory, at least, can claim to encompass all aspects of perverted bodily function in mental diseases, taking in its stride serology, leucopenic function, neurotropic intoxication and all the metabolic processes that are involved in the normal functions of the soma and neuron. The possibilities of extending our knowledge in this sphere of therapeutics are very great, provided we reorientate ourselves and remain biologically-minded. Before completing this very brief review, may I indicate broadly what points appear, to myself at least, to be worthy of exploration ?

1. If a toxin is liberated from the nervous system, can evidence be obtained that this is so in terms of bone-marrow activity and the presence of toxic substances in the blood-stream ?

2. In cases whose nervous system has recovered normal function, what therapeutic means can be devised to recharge the neuron with normal metabolites in terms of remineralization ? Calcium loss is often considerable during narcosis, and the level may have been low previously, tetany having been recorded as a post-narcotic condition. If important ions such as calcium are disturbed, others also may be affected to an extent that render the revived neuron vulnerable. A carefully controlled study of calcium therapy may be worth while.

3. Absorption from the intestine, infective or autotoxic, places a continual strain on the normal detoxicating function of the liver. Disordered action of the colon is so frequent in mental illness that it seems only logical to deal radically and carefully with this neglected tract before narcosis, especially since the capacities of the liver are about to be subjected to a severe strain, as it has much to do in the breaking down of the narcotic. Furthermore, relieving the system of infection, which may be neurotropic, both before, during and after narcosis should at least materially prevent refixation during the post-narcotic period, in which many patients relapse after attaining normality. The foregoing is closely associated with leucogenesis, since deep-seated chronic infection cannot be dealt with if the defences are anergic.

4. Surely the useful but sometimes abused protein shock therapy may have its right and proper place in the scheme of things if carefully controlled by observation on bone-marrow activity ?

5. Experimental neuro-intoxication by the alkaloid mescaline could be studied and made a measure for the relative phylactic efficiency of the numerous barbiturates and other reversible neurotropic agents.

6. Finally, all workers in this field should follow up closely the advances that are being made in our knowledge of brain metabolism. To do so will correctly orientate our imaginations and creative faculties in our search to unravel the complexity of vital interactions between the soma and the neuron.

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