BRITISH MEDICAL JOURNAL:

BEING THE JOURNAL OF THE BRITISH MEDICAL ASSOCIATION.

LONDON: SATURDAY, JULY 1, 1899.

INAUGURAL LECTURE
ON
THE POSSIBILITY OF EXTIRPATING MALARIA FROM CERTAIN LOCALITIES BY A NEW METHOD.

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I cannot help feeling that the Liverpool School of Tropical Medicine has been founded at a most opportune moment—at a moment when science has at last opened the way for an important and interesting adventure—an adventure which is well within our power at least to attempt if not to succeed in: I refer to the experimental trial of a new method, indicated by recent discoveries, for the extirpation of malaria from certain limited areas.

That malaria can often be removed by artificial means has long been proved by actual experience. It is a familiar fact—which I need not dwell upon—that the disease often disappears as the result of drainage and cultivation. We have many examples of this in Europe and America, and, indeed, in England itself, where tracts formerly malarious have now become quite or comparatively salubrious.

Unfortunately, however, there are many malarious localities which we cannot drain and cultivate without a degree of expense which it is impossible to incur; while there are others, as I have myself experienced, where the most virulent malaria remains in spite of both cultivation and drainage. While, therefore, such successful examples as I have alluded to entitle us to admit the possibility of extirpation in some cases, we are forced to add that drainage is neither a sure nor always a practicable mode of dealing with the disease.

As a matter of fact, the efficacy of drainage of the soil as regards malaria is merely the expression of a very familiar law: that this disease, like many others, is connected in some way with humidity; when we remove humidity we often remove malaria. But, nevertheless, drainage must be looked upon as being only an empirical and somewhat gross measure which has been employed by mankind in the absence of any more precise method of extirpation. For instance, in sweeping away all the superfluous waters of a given area, it is possible that we reduce its malaria only because we have happened to remove together with those waters some small pond or puddle which was all the time the true source of the disease, and which, had we been able to detect it before, we could have removed at a hundredth part of the cost. Fortunately, we may now ask with some hope of receiving an answer whether science cannot put us in possession of a more accurate means of detecting the precise focus of malaria in such localities, and, after detection, of removing it.

Unhappily, our efforts to obtain a more scientific frontier of defence against this disease have always hitherto been defeated by our ignorance as to the exact manner in which the infection is produced. For many years, indeed, we have known that malarial fever is due to certain minute parasites of the blood; but how and where these parasites live in external Nature, and how and where they effect an entrance into our bodies we have not been able until lately to discover. Hence, in formulating our epidemiology of the disease we were compelled to fall back upon mere conjectures. Knowing little more than the fact that malaria adheres to certain tracts of country, especially to humid tracts, we assumed that the germs exist at large in the soil, air, or water of such places; that they propagate themselves in these elements; that they are carried by winds from one spot to another; that they rise in mists and exhalations from the soil; that they infect us through the air we breathe or the water which we drink. On what facts were such notions founded? on what exact reasoning? on what precise experiments? On none at all. Vague conjectures, personal impressions, imperfect evidence, were the data on which we were forced to rely—we had none better. The parasites of malaria, so easily detected in the blood of patients, could nowhere be found in external Nature; we had questioned the winds and waters vainly for them; we therefore remained ignorant of how they attack us, and lived without defences against our invisible enemy.

As in many other branches of science, so in respect to malaria, the experimental method of research now compels us to abandon notions based on less trustworthy modes of in-inquiry. In place of our former theories we now possess a clear knowledge of how and where the parasites of malaria live in external Nature, and how and where they enter us. They do not float free in the air or water, as we supposed; they do not rise in mists and exhalations from the soil; they live encased in the bodies of mosquitos, from which they pass into our blood at the moment when the insect inflicts her bite upon us.

It is unnecessary to dwell at greater length on this new discovery than will suffice to convince you of its authenticity. The mosquito theory of malaria has been urged by several writers, during apparently the last hundred years—among others, more recently, by Laveran and Koch; and I may add, it is held by some barbarous tribes who have only too great an experience of the disease. But the idea did not obtain scientific form until Dr. Patrick Manson expounded his famous theory, based on certain recondite changes in the parasite, that this organism requires a suctorial insect for its further development. This induction—which I hold to be one of the profoundest and most important inductions in science—not only gave substance to what was previously little but hypothesis, but showed exactly how the subject was to be attacked by the experimental method. Manson published his views in 1894, and I began the required experiments in 1895. In August, 1897, I first succeeded in cultivating the parasites of malaria in two species of mosquito; and by August, 1898, the development of one of the parasites of birds in the mosquito had been worked out, and healthy birds had been infected by the bites of infected insects—thus completing the life-cycle of these organisms.

In scientific work, however, before any new observation is accredited it must be confirmed and accepted by men of recognised scientific standing. I should therefore mention that my labours were repeated and confirmed last December by Dr. Daniels of the Malaria Commission, who was sent to me to Calcutta by the Royal Society and the Colonial Office[1]; by Professors Grassi, Bignami, and Bastianelli, of Rome[2]; and later by Dr. Koch[3]. Valuable details have been added by these observers and by Dr. MacCallum in America; and the whole researches are now accepted by those distinguished men of science: Dr. Manson[4], Professor Ray Lankester, Dr. Laveran[5], and M. Metchnikoff, and have formed the subject of admirable memoirs by Dr. Nuttall[6] and Dr. Mesnil[7]. All these gentlemen constitute a jury from whose opinion it is impossible to appeal; and the public may therefore safely accept their verdict.

Hence, instead of our vague surmises of yesterday regarding malaria we have now a large body of exact observations to depend upon for our facts. We can follow the actual parasites which cause the disease step by step in their development in the mosquito, and we can detect them in that gland of the insect which secretes the irritating poison injected into us when she bites us. Finally, we can infect any number of healthy birds by allowing infected mosquitos to bite them; and I have heard that the Italian observers have succeeded in infecting healthy persons in the same manner. The research is therefore practically complete.

That these parasites should be able to transfer themselves from a man to a mosquito and back again may however be looked upon as being too wonderful for credence. As a matter of fact, it is nothing exceptional. We have long recognised that many parasitic animals require for their complete development to live in two hosts. Thus, for a few out of many known instances, the common tapeworm, Taenia solium, passes its earlier stage in swine, and then goes on, when swine's flesh containing it is eaten, to its adult stage in human beings. Trichina spiralis has a similar history. Filaria nocturna and Filaria medinensis divide their life between men and mosquitos, and men and Cyclops quadricornis respectively. So with the parasites of malaria, man is the intermediate host, and the mosquito is the definitive host, as it is called; and there is nothing extraordinary in these facts except that the instance is the first of a unicellular animal behaving in this manner.[8]

Similarly the fact that the infection of malaria is produced by the bite of an Arthropod is not without analogy. We know of two important diseases of cattle—namely, Texas cattle fever and tsetse fly disease—which are inoculated, the first by the bite of a cattle tick, Boöphilus bovis, the second by the bite of the tsetse fly, Glossina morsitans.

It is now necessary to touch for a moment on some objections to the mosquito theory of malaria which one occasionally hears of. It is sometimes said that malaria exists in places where there are no mosquitos, and that people who have not been bitten by mosquitos get malarial fever, and the converse. All I can say is that no cases of the sort have yet been substantiated by adequate inquiry, and that the proof of the theory is now so absolute that we are justified in being very sceptical regarding casual statements of this kind. I have often been told that no mosquitos exist in such and such places, but have nevertheless easily found them there by looking carefully for them. Then, again, it must be remembered that certain species of gnats may possibly convey the disease—which will probably explain the former prevalence of malaria in England. Lastly, it must always be remembered that when we speak of malaria being produced by mosquitos we refer only to *malarial* fever, and not to other kinds of fever; and, more than that, we refer only to the *first infection.* Persons once infected with malaria are subject to relapses, which have nothing to do with mosquitos.

Such then are the new facts which science has placed at our disposal. It remains to ask whether they are likely to help us in the prevention of malaria, and if so, how?

Many of those who accept the mosquito theory have emphasised the value of individual precautions against the bites of the insects; I fear it must be said that such precautions will not help us much. A few intelligent people may perhaps escape infection by the scrupulous use of punkahs, mosquito-nets, and so on, and I certainly think that a good deal can be done in this line; but it is idle to suppose that entire populations of malarious areas, often barbarous or semi-barbarous people, will ever trouble themselves to adopt such methods of defence. We must seek some more practical means.

There seems to me to be a distinct possibility of our being able to check, perhaps even to extirpate, malaria in some localities by the extermination of those species of mosquito which carry the disease in that locality. Let me explain my reasons for holding this view.

In the first place, although we are not yet quite certain regarding some details of the subject—such, for instance, as whether malaria is produced only by the bites of the insects and how the parasite is handed on from mosquito to mosquito—we may still, I consider, rest assured of one thing, namely, that the existence of the definitive host of the parasite, the mosquito, is absolutely necessary to the existence of the parasite itself, and therefore to that of the disease. We do not gather this from direct experiment; we gather it from our knowledge of animal life in general and of parasitic life in particular. I have already said that the parasites of malaria, like tapeworms and some other parasites, require two hosts for their development. We are justified then in supposing that if one of these hosts (the mosquitos in the case of malaria) be exterminated, the parasite also must cease to exist. The common tapeworm lives alternately in swine and human beings; if we could ordain the general destruction of swine in a locality, the tapeworm would disappear. The mechanism of all these creatures is so accurately adjusted to their conditions of life that we cannot conceive them as continuing to exist if those conditions be abruptly altered. The parasites of malaria reach maturity in certain species of mosquito; if those species perish, the parasites of malaria must perish with them.

Admitting this, the practical question still remains. Is it at all possible to exterminate the malaria-bearing species of mosquito? Anything like general extermination is, of course, quite impossible; but it may prove possible to get rid of certain species from the more civilised malarious areas, such as towns, cantonments, and plantations. Let me try to explain how.

Needless to say we can never hope to exterminate them by catching and killing them individually. But fortunately there is a very vulnerable stage in their career, before they reach their winged condition; that is, when they are water insects—the little wriggling larvæ found in pots and tubs of water, and in stagnant puddles. These larvæ take about a week to mature in the water. When mature they rise to the surface and become the adult winged insect, and fly away. The females feed on men, cattle or birds, and can live for weeks or even months, laying eggs a few days after each meal. Now it is hopeless to attempt their destruction when they are winged, but our knowledge of their life-history leads us to suppose that if we could make arrangements to empty out once a week all the tubs of water, the ditches, puddles, and wells within a given area, we should be able to exterminate the larvæ within that area, at least for a time—and therefore also we should be able to exterminate, at least to a great extent, the adult mosquitos.[9]

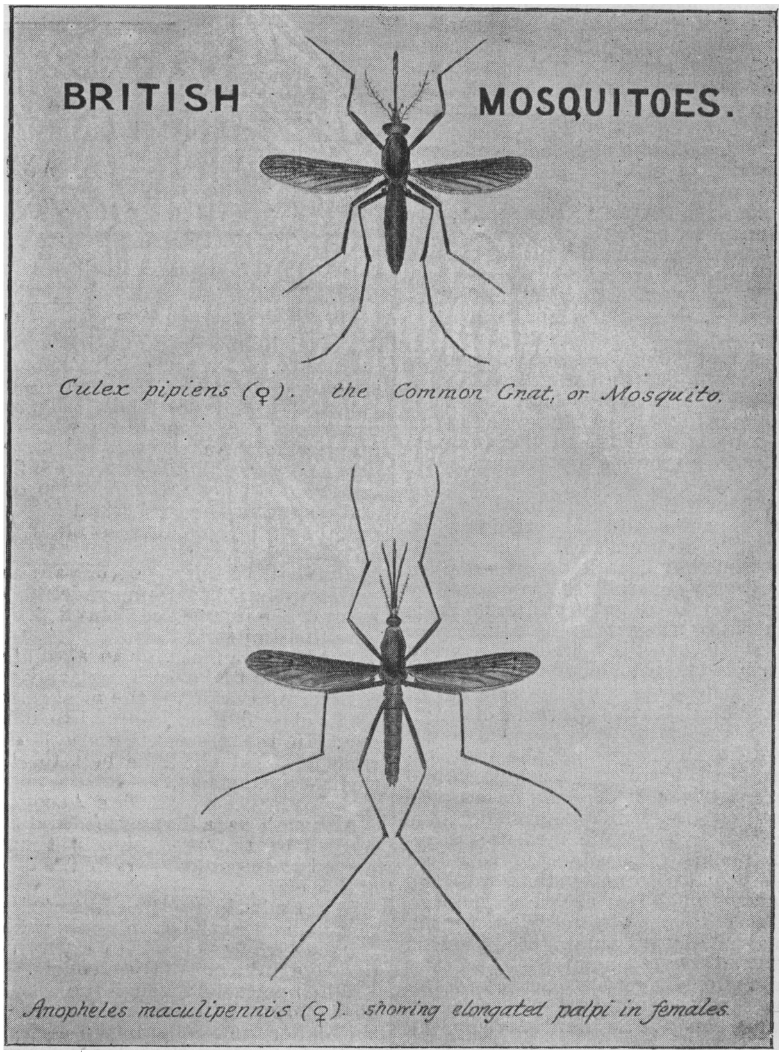
I know, from my own experiences in India, that private houses may often be kept comparatively free of mosquitos simply by banishing stagnant water from the premises. But a public measure of the same kind would be much more difficult. In many large native towns in the tropics, for instance, the pots, tubs, cisterns, wells, drains, ditches, ponds, and puddles are so innumerable that I fear it would prove a hopeless task, even to the most efficient municipality, to deal with all of these once a week. The case might be different, however, were we called upon to deal only with certain species of mosquito—say, for example, with mosquitos which do not breed in these innumerable pots and tubs of water, but which confine themselves to a few small puddles of a certain description, which can be easily found and filled up. Here we might hope to do something.

Fortunately, in order to extirpate malaria, it will not be necessary to declare war against all mosquitos in general. We already know for a fact that only certain species can carry the disease. If it prove to be the case, as I think it may prove, that these particular species can breed only in a few isolated collections of water, then we may expect to find ourselves in possession of a cheap and effective means of extirpating malaria, at least from the more civilised and therefore the more important areas.

According to my observations in India the commoner kinds of mosquito there belong to two genera of the zoological family of the Culicidæ—namely, genus Culex and genus Anopheles. The commonest species, those which swarm in almost all Indian towns and villages, appear to belong to genus Culex. They are distinguished zoologically by the females possessing short palpi, and more popularly by generally having plain unspotted wings, and by sitting against walls with their bodies hanging downward. They seem often to bite birds as well as men. Their legs and bodies may be variously striped (brindled mosquitos) or unstriped (grey mosquitos). Their eggs are laid on water; their larvæ or grubs, so far as I have observed, float head downward when resting on the surface of the water; and are generally able to breed in pots and tubs of water, cisterns, wells, and drains—that is, they seem to prefer artificial collections of water such as these to natural collections, such as rainwater, puddles, and ponds. It is owing to this fact that they are found in such large numbers in Indian towns and houses, and, indeed, the commoner species may be described as *domestic* mosquitos in the same sense as we call the common housefly Musca domestica. Cursory observers, when they mention mosquitos, generally talk of this genus.

Mosquitos of the other genus, Anopheles, are very different, and may be called *rural* mosquitos. So far as I have been able to observe, their larvæ are scarcely ever to be found in vessels and other artificial collections of water, but only in natural ponds and puddles; hence they are not so common in towns as genus Culex, while they may often be very plentiful in villages and plantations. To find the adults I used to search stables and cattle byres. The genus is distinguished from Culex by possessing long palpi in the female. The wings are generally spotted on the anterior edge. The body is shaped somewhat like that of the humming bird moth, and when the insects sit on a wall the body projects outward. They bite cattle as well as men, but I could not easily persuade them to bite birds. Their eggs can be affixed to hard surfaces. The larvæ do not float head downwards like those of Culex, but float flat on the surface of the water like sticks, an important difference—due to the absence of a breathing tube in Anopheles—which enables us to distinguish the grubs at a glance, and therefore the pools in which they breed.

While I have always been able to obtain the larvæ of Culex without difficulty — since they occur in numerous vessels and drains holding water—I have generally found it hard to get those of Anopheles. For example, in an area of several square miles in Secunderabad, although adult Anopheles[10] were very common, we could find the larvæ only in a single small puddle; and I experienced the same thing in Calcutta, where they occurred in a pond, and in Nowgong, Assam, where they were found in an old boat full of earth; while in Naxalbari, in the Darjeeling Terai, a very malarious place, although there were swarms of Anopheles, I could not find their grubs at all.



British mosquitos (Culex and Anopheles). From a drawing by Mr. Ernest Austen, Dipterist to the British Museum, Natural History Department.

The reason for the scarcity of the breeding-pools of Anopheles appears to be that the puddles (*a*) must be large enough to be permanent for a few days to allow the larvæ to mature; (*b*) must not be so large as to contain minnows (which devour the larvæ with avidity); and (*c*) must not be liable to be scoured out by every shower of rain. In India minnows are found in almost all collections of water on the ground, such as running water, lakes, large ponds, tanks, and ricefields, often down to the smallest pools of rainwater; while puddles which are too high-placed or isolated for fish are apt to dry up during fine weather, or to be scoured out when there is rain. In short, the grubs of puddle-breeding mosquitos, as we may call them, are subject to so many dangers that I suppose few haunts can afford them the requisite shelter.

I give these facts as I found them in India; but should add that my studies of mosquitos were far from being formal enough to cover all the various species.

To return, then, to our original question—if I were asked whether it was possible to exterminate mosquitos, I should reply in the negative in respect to Culex, while I should think it probably possible to exterminate Anopheles in certain localities. The haunts of Culex appear to be too common to be obliterated; those of Anopheles rare enough to be dealt with by local agencies.

I will now direct your attention to a very important point—the significance of which you will readily be able to appreciate. There are many reasons for thinking that human malaria is not conveyed by genus Culex, which I think cannot be exterminated, but may be conveyed by genus Anopheles, which I think can be exterminated.

During several years in India I endeavoured to cultivate human malaria in many species of mosquito. I tried many species of Culex, including the commonest ones; all the experiments failed. I also tried five kinds of Anopheles. Three of these failed, but, on the contrary, two succeeded.

Unfortunately these successful experiments were the first I performed, and I was suddenly moved to another station just as I had reached success; so that I cannot give precise names to the two species of mosquito employed. Nevertheless I know for certain that both belonged to the genus Anopheles, and that both can carry human malaria.[11]

Now Grassi, Bignami, and Bastianelli have also succeeded in cultivating the germs of human malaria in mosquitos in Italy; and it is a fact well worthy of attention that the species of mosquito with which they have succeeded is a third species of Anopheles, namely, according to Grassi, Anopheles claviger (Fabr). Hence the three species of mosquito which we are sure can carry human malaria all belong to genus Anopheles. Compare Grassi[12].

But there are more general reasons for exonerating Culex, or indeed all mosquitos which breed chiefly in artificial collections of water, from producing malaria. Such mosquitos necessarily abound in proximity to man—that is, in towns and houses; whereas malaria is notoriously rather a disease of the open country, and even of uninhabited country, thus coinciding better with the distribution of Anopheles. Again, malaria is connected with rainfall, just as Anopheles appear to be; while Culex depend for their existence rather on artificial irrigation, drains, and wells, and are often more prevalent in the dry than in the wet season. Lastly, we know that malaria can often be removed by drainage of the soil; we can understand this on the theory that the disease is produced by Anopheles or other mosquitos which breed in puddles on the ground, but not on the supposition that it is produced by insects which breed in vessels of water. Thus, whether the dangerous mosquitos are confined to genus Anopheles or not, the inference still remains that they are at any rate puddle-breeding mosquitos, and not pot-breeding ones—that is, that we may hope to be able to exterminate them in the more populous and civilised areas.

A strong argument to the same effect may be adduced from the general laws of distribution of malaria. The disease is never uniformly distributed even in small areas. Isolated spots, individual plantations or barracks or villages, even single houses, are often known to be more malarious than their surroundings. This argues not only that malaria is not due to the common mosquitos which are found almost everywhere, but that it is caused by mosquitos which have a distribution similar to that of the disease whose haunts are also comparatively rare and isolated.

Before concluding, I must add some statements having a practical bearing. (*a*) We can detect the dangerous species of mosquitos in a given locality by a perfectly certain method, namely, by ascertaining according to Manson's induction whether the parasites of malaria will live in them or not. (*b*) We can detect their breeding grounds by searching for their larvæ. If the dangerous mosquitos prove to be confined to genus Anopheles, the problem will be much simplified, and it will be advisable to declare war against the whole genus. The larvæ of this genus can be distinguished by any intelligent European by the fact that they float flat on the surface of the water, and the adults can be generally distinguished by their having spotted wings. (*c*) In order to obliterate pools which breed dangerous mosquitos, they must be filled up or drained away. As I have said, mosquitos scarcely ever breed in large bodies of water, because these contain fish. To kill larvæ in wells, some appropriate drug must be sought for, but I think it unlikely that malaria-bearing insects often inhabit wells.

To conclude, then: It will be observed that the practicability of eradicating malaria in a locality by the extermination of the dangerous mosquitos in it depends on a single question—Do these mosquitos breed in spots sufficiently isolated and rare to be dealt with by public measures of repression? I am afraid that it is impossible to give a final answer to this question as yet; we do not yet know all the dangerous species of mosquito, much less are we acquainted with all their habits. But I have addressed you at such length on this subject to-night because I am inclined towards giving an answer in the affirmative to the question. At any rate, in view of the mischief wrought by the disease in warm countries, I certainly think that we should make every effort to ascertain whether or not we can give an affirmative answer to it.

For a concrete example, suppose we were to discover by accurate investigation that all the malaria in a large town—say on the coast of Africa—arises from a few small puddles which can be obliterated at the expense of a pound or two, would not this discovery repay our exertions? and, further, if we could next extend our operations to other towns—to numerous towns—in the tropics, should we not be more than repaid for our exertions? At all events, the question can be decided only by experiment; and the experiment is well worth making.

NOTES AND REFERENCES.

1 Daniels, *Proceedings of the Royal Socieiy*, vol. lxiv. 2 Grassi, Bignami, and Bastianelli. *Atti d. R. Accad. dei Lincei*, etc., Dec. 22nd, 1898. 3 Koch, *Deut. med. Woch.*, 1899, No. 5. 4 Manson, BRITISH MEDICAL JOURNAL, Sept. 24th. 1898. 5 Laveran, *Bull. de l'Accad. de Med.*, Jan. 31st, 1899. 6 Nuttall, *Cent. f. Bakt.*, etc., Band xxv, 1899. 7 Mesnil, *Rev. Gén. des Sciences*, March 30th, April 15th, 1899. 8 I should add, however, that the parasites of malaria are probably capable of passing from mosquito to mosquito, as well as between mosquitos and men. 9 Mosquitos seldom fly far, and if we observe them anywhere in large numbers we may be sure that their breeding-ground is not distant. Hence the extermination of larvæ within a given area will generally imply also the extermination of the adults. 10 Of the small light brown malaria-bearing species mentioned further on. 11 One was a large dark brown species, and the other a small light brown one; both had spotted wings and the general characters of Anopheles. They had been fed on a patient containing crescents, *vide* Ross, BRITISH MEDICAL JOURNAL, December 18th, 1897, and February 28th, 1898. The "grey mosquito" (of Culex—probably C. pipiens) referred to in this paper as showing "pigmented cells" after having been caught biting a case of tertian, had probably become infected from previously biting a bird with Proteosoma Grassii (Labbé). I failed subsequently in cultivating tertian in this species, but succeeded in cultivating P. Grassi in it. My negative experiments with Culex were tried with all kinds of malaria. 12 Grassi, *Atti d. R. Accad. dei Lincei*, etc., vol, vii, 1898.

THE CROONIAN LECTURES

ON

SOME POINTS CONNECTED WITH SLEEP, SLEEPLESSNESS, AND HYPNOTICS.

Delivered before the Royal College of Physicians of London.

BY JOHN BUCKLEY BRADBURY, M.D.CANTAB.,

Fellow of the College; Downing Professor of Medicine in the University of Cambridge; and Senior Physician to Addenbrooke's Hospital.

LECTURE II.

AN ideal hypnotic is one that will produce sleep of sufficient duration, under all conditions, without ill-effects or after-effects; we know of no such remedy at present, and it is doubtful if we ever shall. The administration of hypnotic drugs produces a condition which is closely allied to, if not identical with, a pathological state. Few, if any, of these drugs possess a purely selective influence on the cerebral cells, but even if they did, depression of other organs—circulatory and respiratory—would result from an action on their centres, and the presence of disease might determine a fatal effect of an otherwise non-lethal dose. Moreover, the variability of the individual, the presence of pain and other conditions, altogether preclude us from expecting to attain a precise adjustment of the induced cerebral depression so as never to overpass the limits of safety.

But if we cannot find an absolutely harmless hypnotic, at least we can find a comparatively safe one, and it is our duty to determine which is the most reliable and the least toxic.

The classification I intend to follow is mainly a chemical one. In the present lecture I shall deal with synthetic remedies, and it will be best to start with the simplest of them—the alcohols.

THE ALCOHOLS.

Although as a hypnotic ethyl alcohol is not largely prescribed by the profession, yet with its homologues it has played an important part in the discovery of newer remedies of this class.

[After alluding to the effect of alcohol on isolated organs, on muscle, and on the circulation, the lecturer continued:]

I shall confine myself to my own experiments[1] on the comparative influence of the alcohols.

When perfused through the vessels of a water tortoise each alcohol causes a transient dilatation, followed by contraction, the higher the alcohol in the series the greater is the effect. Methyl and ethyl alcohols are not very active.

Hypnotic action and toxicity follow the same order as the effect upon simple tissues as Dujardin-Beaumetz and Audigé have shown in regard to toxicity.[2] More exact results are those obtained by Joffroy and Serveaux, who recognise two kinds of toxicity—a true toxicity and an experimental one. True toxicity they define as the smallest quantity of substance per kg. body weight, which will bring about death after a short delay. By experimental toxicity they mean the amount of alcohol necessary to cause death when the injection is continued up to the final stoppage of the respiration. The numbers in this case were found to be: Methyl alcohol, 25.25; ethyl alcohol, 11.70; propyl alcohol, 3.40; iso-butyl alcohol, 1.45; amyl alcohol, 0.53. With the exception of the relative innocuousness of methyl alcohol, this agrees on the whole with the experiments of previous