THE POSSIBLE SUBSTITUTES FOR COCAINE.

ABSTRACT OF REMARKS INTRODUCING A DISCUSSION
AT THE ROYAL SOCIETY OF MEDICINE,*

BY

H. H. DALE, M.D., F.R.S., F.R.C.P.,

HEAD OF DEPARTMENT OF BIOCHEMISTRY AND PHARMACOLOGY UNDER
THE MEDICAL RESEARCH COUNCIL.

It may seem strange that the question of replacing cocaine by artificial substitutes has excited interest, even in extra-medical circles, which is not aroused in the case of other alkaloids, even when these are, like cocaine, dangerous drugs of addiction. We must admit, I think, that the case of cocaine is in some respects unique. There are other drugs of addiction; but cocaine appears to be the only one in which the therapeutic value depends upon an action of a different type from that which leads to the vicious habit. In therapeutics only its local actions have any serious value, whereas the action desired by the addict is one produced, after absorption, upon his central nervous system. So far from having a positive value in therapeutics, these effects of cocaine after absorption complicate its use in medicine and surgery by producing undesirable and even dangerous symptoms. Theoretically it is not impossible, or even improbable, that a substance might be produced having all the valuable properties of cocaine and none of its harmful or dangerous ones. Cocaine, in comparison with many medicinal alkaloids, is a relatively simple substance, and its structure readily lends itself to the formation of artificial derivatives, and of substances departing more or less widely from its constitution, but retaining the structural features which experiment has shown to be definitely associated with its essential anaesthetic action. Professor Gibson, who is to speak later, will doubtless have something to say concerning the chemical aspect of the problems involved. I take it to be my function rather to indicate some more general points on which discussion may be valuable, and concerning which practical evidence is required. If convincing evidence were forthcoming that a substance existed having all those local effects of cocaine which assist the surgeon, a lower immediate general toxicity, and no tendency to produce addiction, I suppose we may take for granted the adoption of such a substitute by the medical profession, and the rapid fall of cocaine into disuse. If we knew of such a substance, we should be anxious to bring it to the notice of our colleagues, and to advocate its adoption, if advocacy were needed. The purpose of our discussion is to consider the various substances put forward as substitutes for cocaine, and to discover how far any one of them, or all of them together, can thus fulfil its functions and avert its dangers.

Properties of Cocaine.

It will be convenient to have in mind, during our discussion, a list of the properties of cocaine itself; distinguishing those which are essential for all its applications, those which give it special value for particular purposes, and those which are wholly undesirable. I will number them for convenience of reference.

1. We begin, of course, with its powerful and long-persistent local anaesthetic action, including therewith its power of penetrating the tissues, which enables it to produce anaesthesia of relatively deep structures, when it is superficially applied to the mucous membrane, whether of the conjunctiva or the respiratory passages.

2. Next in order of importance we have its property of producing, when locally applied to a mucous membrane, a constriction of the small blood vessels, producing ischaemia and deturgescence, which have great value for certain surgical purposes. With this we may mention its mydriatic action.

3. Though not entirely free from irritant properties, cocaine shows little tendency to irritate or devitalize the tissues in an area into which it has been injected.

We come now to its undesirable properties.

4. Cocaine is a somewhat unstable substance, so that its solutions cannot be sterilized by boiling without danger of hydrolysing it into benzoic acid and methyl-ecgonine, with destruction of the local anaesthetic action.

5. Cocaine is a dangerously toxic substance when absorbed into the general circulation. The danger of such absorption severely limits its use for producing anaesthesia by injection, and is by no means completely absent when the application is made to intact mucous membranes, except when small quantities of dilute solutions are used. The symptoms produced comprise a primary stimulation of the brain, with acceleration of cerebral processes, loss of sensation of fatigue, feeling of unwonted efficiency and general euphoria. This is succeeded by restlessness and garrulity, accompanied by accelerated respiration, quickening of the heart beat, rise of the arterial blood pressure and of the body temperature. If the toxic action progresses further, these stimulant actions are followed by depression; the blood pressure collapses, the heart beat becomes slow and feeble, the skin pale and cold, consciousness is lost, and death may ensue from paralysis of the respiratory centre.

6. Lastly we have the fact that the primary stimulant effect of a not immediately dangerous dose, when experienced by a subject whose self-control is weak, is apt to leave an urgent desire for its repetition, especially as a relief from the depression which follows the feeling of exalted vitality and general euphoria. I need say no more concerning resultant addiction and its deplorable effects.

Substitutes in Local Anaesthesia.

From the very long list of local anaesthetics which have been put forward as substitutes for cocaine, we may select for consideration only those which have had some measure of success. We may further omit the substances of low solubility, such as orthoform and anaesthesin, which are only suitable for use as analgesic dusting powders. We are left with the eucaines, of which only beta-eucaine has had practical success; tropacocaine, the only natural alkaloid which has had any measure of success in this direction; stovaine and the closely related alpine; and, lastly, novocain and its higher homologue, butyn. Of substances having no chemical similarity of any kind to cocaine, it should be mentioned that quinine, in the form of the double salt with urea, has been used for anaesthetizing the deeper layers of the body wall in infiltration anaesthesia. But, since cocaine itself would hardly be used in that manner now, we cannot consider quinine as a serious rival. I imagine that the same is probably true of benzyl alcohol and phenyl ethyl alcohol. Some years ago there was quite a series of publications in American pharmacological and medical journals advocating the use of these simple and relatively cheap substances as local anaesthetics, either by local application or for infiltration anaesthesia. At the time of the first publications, early in the war, I made a number of experiments in the laboratory with very disappointing results. I supposed that my technique was somehow at fault; but the fact that, with substances available, which are so cheap, so stable, and so free from danger as these, new local anaesthetics of the cocaine type are still being sought, even in America, makes me suspect some excess of enthusiasm in the earlier advocacy.

Comparison of Substitutes.

Confining our attention, therefore, to the substances having some, even if remote, similarity to cocaine in chemical structure and a general similarity in their type of action, we have to compare them with cocaine with respect to the desirable and undesirable properties which I mentioned above.

(1) In intensity and persistence of local anaesthetic action, it seems to be generally agreed that cocaine stands as yet unrivalled, except, perhaps, by the recently introduced butyn. Nor can the admittedly weaker and more

* The discussion which followed the reading of the opening paper is reported at page 520.

evanescent action of such an established substitute as novocain be wholly compensated by using it in stronger solution. Novocain appears to be much more rapidly destroyed in contact with the tissues, so that even when a satisfactory superficial action is obtained it does not penetrate deeply. Tropicocaine has been said by some to be as active as cocaine with local application, but its effect is more evanescent. For butyn an equal anaesthetic efficiency with cocaine has been claimed by American observers, but this claim has not hitherto received consistent support in this country. Further evidence as to its efficiency is very desirable, and it may be hoped that this discussion will produce some.

(2) I have found no record of even a claim, for any of the suggested substitutes, that it resembles cocaine in constricting the blood vessels and producing shrinkage when applied to a mucous membrane. For some surgical purposes this action may be undesirable; there is no doubt that for others it is considered valuable, and even indispensable. It is important that a discussion like this should produce evidence as to whether any of the available substitutes has this action of cocaine, and, if not, whether the defect can be compensated by mixing the locally anaesthetic substance with a suitable proportion of adrenaline. Similarly, it would be of interest to hear, from our ophthalmological colleagues, what importance attaches to the mydriatic action which cocaine possesses but apparently none of the substitutes.

(3) Many of the suggested substitutes for cocaine have the defect that their anaesthetic action on peripheral sensory nerve endings is complicated by a much more seriously harmful action on the surrounding tissue cells than that which cocaine produces. Such an effect is, of course, apt to be intensified when the action is localized by the presence of adrenaline. The data which I have seen suggest that this irritant and devitalizing action compromises the value of eucaine, tropacocaine, stovaine, and, especially, alypine. Novocain appears to be remarkably free from it, and one would expect the higher homologue, butyn, to show a favourable record in this respect.

(4) All the suggested substitutes appear to be more stable than cocaine to boiling in watery solution.

(5) Most of the substitutes have less general toxicity than cocaine. Aypine is probably an exception, and, being practically as toxic as cocaine on absorption, and much more irritant locally, it is not likely to have advantages for many purposes. Eucaine, tropacocaine, stovaine, and novocain are all much less liable than cocaine to produce bad symptoms if absorbed into the general circulation. The position of butyn is yet uncertain, and it may be hoped that this discussion will make it clearer. Animal experiments seem to have indicated that it is even more toxic than cocaine itself; on the other hand, it was claimed that in human therapeutics its use had been singularly free from bad symptoms resulting from accidental absorption.

Leaving for the moment the question of danger of the drug habit, we find that, of the available substitutes, several are much weaker in general toxicity and therefore safer than cocaine, and that some of these are sufficiently potent and penetrating in anaesthetic action. But those which have sufficient potency and penetration appear to have the drawback of irritating and devitalizing the tissues, whilst novocain, which is ideal in this respect, is deficient in power, penetration, and persistence of effect. None appears to have the vaso-constrictor action of cocaine or to dilate the pupil. It is obvious that, for some of the uses of local anaesthetics, one or another of these deficiencies may be immaterial; and that, by choosing for each separate purpose the appropriate substance, cocaine can be, and to a large extent has been, replaced by safer substitutes. I suppose that for infiltration anaesthesia and for nerve blocking novocain meets most needs. For producing analgesia by intrathecal injection stovaine and tropacocaine have been largely used, and I suppose that cocaine has been altogether abandoned for this purpose. It is obvious that each special branch of practice must speak for itself; and I would suggest that the aim of the discussion should

not be merely to discover whether there is any one substance which can replace cocaine for all purposes, but whether for each of the different uses of cocaine there is any less dangerous and perfectly efficient substitute; in other words, whether there is any use of cocaine for which no less dangerous substitute exists which can efficiently produce the desired effect even when associated with adrenaline.

In speaking of "less dangerous" substitutes I have in mind not merely the danger of immediate toxicity, but the much more subtle danger of addiction. It is common knowledge that the problem created by the cocaine habit has led the Minister of Health to appoint a special committee to discuss this question, the reference to the committee being "to investigate the comparative value, for therapeutic purposes for which cocaine is at present used, of various possible substitutes, and the evidence as to risk, if any, of such substitutes becoming drugs of addiction." As a member of that committee, my duty is simply to ask for information, and not to express any opinion which could even seem to anticipate the committee's conclusions.

The Danger of Addiction.

On the question of possible addiction to the substitutes, I think I can state, without indiscretion, that inquiries which I have made myself, from those most likely to know, in countries where drug addiction is widely prevalent, have failed to elicit evidence of a case of addiction to any of the local anaesthetics other than cocaine. Unfortunately the absence of recorded cases hitherto does not exclude the possibility, and it would be of great interest to know whether any of the substitutes has been found to produce a mental exaltation and euphoria comparable to that produced by cocaine, and providing the basis for its habit-forming property.

Another question of importance in this connexion is that of the extent to which the proper use of cocaine in medicine and surgery involves the danger of producing a drug habit. This again involves the question as to what is a proper use of cocaine. Probably there are those present who can quote cases in which the prescription of cocaine, for application by the patient himself, has resulted in the formation of a vicious habit. Such cases may be rare, but I gather that evidence of their existence can be produced. On the other hand, it would be of great interest to know whether a single application of cocaine by the medical man himself, to produce a local anaesthesia for operation or to facilitate examination, has ever been known to result in the acquisition of the habit by the patient. If not, the question necessarily arises whether cocaine itself is indispensable for any of the other purposes for which it can now be used and prescribed, or whether these other uses could be met by one or another of the substitutes. The practical question is, in brief, whether medical practice would in any direction be materially hampered if the use of cocaine, short of its complete abolition, were limited to direct application by the medical man himself, with prohibition of dispensing or prescription for the patient.

The title given to me for the discussion was "The possible substitutes for cocaine." I have assumed that the council of the society intended us to limit our discussion to those which are hitherto available. The only practical question for us at present is whether any of these, or all of them together, so far fulfil the functions of cocaine that medicine and surgery could do without it. It is obvious that no negative answer, given to this question at the present time, could be final. The synthesis of cocaine itself has only recently been completed, and has resulted in the production of a series of isomeric cocaines. There is still a large field of synthesis unexplored, and at any time the ideal local anaesthetic may appear—potent, penetrating, astringent, and at the same time free from dangerous properties, whether of immediate toxicity or of habit formation. Our business is not, however, to speculate on the future, but to decide, on evidence, whether ideal substitutes, or reasonably efficient substitutes, are now available; and, if not, whether the use of cocaine itself can be so restricted as to minimize its dangers without real detriment to practice.