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THE INFLUENCE OF ALCOHOL
AND OTHER DRUGS
ON FATIGUE

THE CROONIAN LECTURES DELIVERED AT THE ROYAL
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THE ACTION OF DRUGS.

Experiments on the action of drugs in fatigue may be carried out by two methods. In one method a certain amount of work is done every day for several periods, each of a week or fortnight, or longer. During some periods the drug is taken

every day, but not at such a time of the day as to show its immediate effect on the work, while during other periods there is complete abstention from the drug. By this method there is tested the influence on the capacity for work of the general condition produced by the ingestion of the drug. No such work has hitherto been done on the capacity for muscular work; but it has been employed by Kraepelin and his school to test the influence on the capacity for mental work of alcohol taken daily for a certain period.

The other and more usual method by which the action of drugs is tested is to do a certain amount of work every day, taking a dose of the drug on some days and abstaining on other days. In this way, then, is tested not only the immediate action of the drug on the capacity for work, but by prolonging the work of each day the influence of the drug may be followed for many hours. This method is that which has usually been employed in the work I shall bring forward in these lectures.

The two methods could be combined; and this may be done most easily by comparing the work of the normal or control days during a drug experiment of the second class with the work of a similar series consisting wholly of normal days.

I have now described the general character of the methods which are employed in the study of muscular and mental fatigue, and can turn to the consideration of some aspects of the experimental study of fatigue which are of especial importance in estimating the influence of drugs.

We shall see later that the most varied methods have been used by different workers in studying the action of drugs. A common method has been to work to exhaustion, and then to see if the administration of a drug is able to call forth a further amount of work; others give a record of work which they state is their normal amount, and then give the result under the influence of a drug, but provide no indication of the relation between the supposed increment or decrement produced by the drug and the normal variations which occur from day to day.

The most satisfactory method, which was first adopted in a really systematic manner by Kraepelin, is to carry out work on a number of successive days (or days at regular intervals), keeping all conditions exactly alike on the different days, except that on some a drug is administered. The drug may be given before beginning the work of each day, but there are certain practical difficulties to which this procedure is subject. In many cases the drug-days will give an average which deviates from that of the normal days so greatly that there can be no question as to the action of the drug; but in other cases the deviation may be so slight that the question arises whether it may not be within the average deviation of the normal days from one another. There are, of course, definite methods for ascertaining the relation between a given difference and the probable difference due to normal variations, but their application in this branch of study is rendered very difficult by the existence of practice, etc.—*i.e.*, we have to do not merely with a number of days which differ from one another by chance variations of daily disposition, etc., but with days which differ owing to the existence of certain more or less regular influences which, though they no doubt follow definite laws, are not yet sufficiently understood to allow the application of statistical measures.

This difficulty may, however, be overcome in large measure if the drug is given at some period after the work has been begun, so that the results can be expressed in relation to the initial performance before the drug has been taken. This latter method is that which I have usually employed.

In carrying out an experiment of this kind, extending over a number of days, it is essential that all the conditions of life be kept as constant as possible. The same amount of sleep must be taken every night, the meals must be of the same kind and at the same times every day, the same amount of exercise must be taken, and the same amount of other work done. To do experimental work of this kind really satisfactorily means to most people that they must cut themselves off from many of the ordinary pursuits of life so long as the experi-

ments last. In my own case the fact that my occupation involves very different amounts of work on different days has made it impossible, as a general rule, to carry out any experimental work during term-time, and my own most satisfactory work has been done in the country, away from all possible sources of disturbance.

In the case of muscular work, the necessity for rigorous equality of the conditions of life is perhaps not so great as in the case of mental work; but here the more similar the conditions can be kept, the more likely is it that satisfactory results will be obtained.

It must be understood that these rigorous conditions are not necessary for the crude determination of the action of large doses of drugs; but it is not with such work that I am now concerned. It is my object in these lectures to consider the methods to be followed in the endeavour to ascertain the effects of those doses of drugs which are used either for dietetical or therapeutical purposes, and for such an object unequivocal results can only be expected if the conditions of life are kept as rigorously uniform as possible.

A difficulty which arises in drug experiments is due to the practice of taking as part of the normal diet substances which have an effect on the capacity for work; and this difficulty becomes especially great when it is one of these drugs which is the subject of experiment. There are two possible lines of action: the use of the substances may be wholly discontinued before the experiment begins, or the experimenter may continue to take them, but in exactly the same quantity every day and at exactly the same times, while he may perhaps diminish their amounts. The former procedure, which has been adopted by several workers, is open to a serious danger, to which my attention was called by my own experience. I began my work on drugs with an experiment on the effects of caffeine, and discontinued the use of tea and coffee shortly before the experiment began, having previously taken them in diminished quantity. The act of giving up the use of these substances was followed by loss

of energy, which greatly interfered with the success of the experiment, and a later repetition of the experience left little doubt that the condition was due, at any rate in part, to the discontinuance of the use of tea and coffee. My reaction was probably exceptional; but a condition which is so pronounced in one person is probably present to some extent in all, though it may be masked by other variations in bodily and mental health. Indeed, it seems only natural that the sudden cessation of the habitual action of such a substance as caffeine must have a decided effect on those vital processes on which it has any influence.

If, in investigations on the effect of such a substance as alcohol in one accustomed to it, the use of the active substance is only given up shortly before the commencement of the experiments, there is a further danger. Even in those who only take such a substance in moderate amounts, its disuse is probably followed in some degree by the craving which is so pronounced after discontinuance of large amounts, and, slight and hardly noticeable as this craving may be, it may yet be sufficient to produce an obvious effect when the article of which the person has been deprived is administered experimentally. The effect of the substance given experimentally may be the result, not of its normal physiological action, but of the satisfaction of a craving. For these reasons it seemed best to give up completely the use of all the stimulating articles of diet in ordinary use for several months before beginning my next research, and much of the work to be described in these lectures was done more than a year after the use of alcohol and caffeine-containing articles of diet had been given up, except for experimental purposes or on such rare occasions that there could be no question of habituation. So drastic a procedure is not likely to attract workers to this subject; and though it has been followed also by Mr. Webber, who has been my co-worker in many of the researches to be described in these lectures, I have been content in other cases to allow the continued use of tea, coffee, alcohol, or tobacco, but in equal amounts and at the same times every day, and

wherever possible not till after the experimental work of the day has been done.

Another difficulty arises in connexion with practice and training. Some recent workers have insisted on the necessity for long-continued training before beginning to use ergographic curves as objects for scientific study, and one, Hellsten, trained for many months before he began to study the action of drugs.

By following such a rule it seems to me that a great experimental opportunity is being neglected. One of the features of the work of untrained muscle is the occurrence of painful or unpleasant sensations ; and since one of the definite problems in connexion with the effect of drugs on fatigue is how far they act through their influence on the sensations of fatigue, comparative work on trained and untrained muscle may be of great value. In my own work, therefore, I have tested the influence of drugs in various conditions of training, and in every case introspective notes have been recorded to show whether painful or other unpleasant sensations have been experienced during the course of the experiment.

I can now pass to a feature of method in which lies the chief interest of the new work I hope to bring before you—a feature designed to eliminate the influence of certain psychical factors which have undoubtedly been allowed to affect the results of nearly all who have experimented on the action of drugs. Many of these workers have considered the possibility that their results may have been influenced by suggestion, or of bias towards results which were to be expected theoretically, and some have shown that effects similar to those following the administration of a drug may be the consequence of the administration of a wholly inactive substance which is supposed by the subject to be the drug in question. Few, however, have adopted the obvious precautions which such considerations suggest ; Schumburg¹ and

¹ *Arch. f. Anat. u. Physiol.*, Physiol. Abth., Suppl. Bd., 1899, S. 289.

Sobieranski¹ are the only workers with drugs² who have used any kind of control-substances, and even they do not make it clear that the control mixtures or injections they used were entirely indistinguishable from those containing the active substances.

The factor which previous writers have considered under the title of 'suggestion' is far from being the only source of error in work on the action of drugs. Féré has shown that the sensory stimulation involved in the act of taking a drug into the mouth and swallowing it may have a very decided effect on the amount of work executed with the ergograph, but even this knowledge did not lead him to adopt any control in his numerous researches on drugs.

There is, however, another factor which is probably more important than either sensory stimulation or suggestion—viz., the interest and excitement produced by taking a substance when the discovery of its effect is the motive of the whole experiment. The ergographic curve is an extremely delicate reagent to any form of mental excitement. Any novelty in the course of an experiment may have a very decided effect on the amount of work. The interest of a conversation, the knowledge that the performance is being watched, the view of the weight rising as one works or of the formation of the ergogram on the drum, or any other variation in the routine of the daily experiment, may have very obvious effects on the amount of work. Similarly, the knowledge that it is the first or last day of an experiment may produce a distinct increase in the amount of work, so decided that I now always adopt the procedure of working for one or two days before and after the period which is to provide the proper data for the experiment.

If such a condition of interest as that arising from its

¹ *Centralbl. f. Physiol.*, 1896, Bd. x., S. 126.

² Schumburg has also used dulcin as a control substance in work on the action of sugar (*Zeitschr. f. diätetisch. u. physikal. Therapie*, 1899, Bd. ii., S. 185), and irreproachable work from this point of view has been done by Pregl (*Arch. f. d. ges. Physiol.*, 1896, Bd. lxii., S. 379) on the action of orchitic extract.

being the first or last day of an experiment, or that resulting from the view of the weight rising as the finger contracts, can have very appreciable effects on the amount of work, it is clear that so interesting an occurrence as the administration of a drug must have a decided influence, and the interest so aroused will probably be equally great whether the nature of the drug is unknown, so that there is an element of mystery in the occurrence, or whether its nature is known. When in the latter case the subject is himself the experimenter, keenly interested in the possible results of his experiment, this factor of interest must often be very strong.

In my first experiment with a drug, I soon became aware of the existence of such interest. I noticed that the days on which I took the drug interested me more than the normal days on which nothing was taken. I felt at once stimulated by the fact of having taken the substance, the action of which I was trying to test, and it was obvious that I had no means of telling whether any effect which might be produced was due to this interest or to the proper physiological action of the drug. In all future experiments I therefore determined to endeavour to disguise the days on which the drug was being taken and all the new work to be described in these lectures has been carried out with the use of control mixtures which have usually been wholly indistinguishable from those containing the active substances. The subject of an experiment has taken every day at some time in its course a dose of a mixture, and has been wholly unaware whether he has taken the substance which is the motive of the experiment or some inactive imitation of it. These control mixtures have in most cases been prepared for me by Dr. W. E. Dixon, to whose help in this direction I am very greatly indebted. In some cases in which I have myself been the subject of the experiment, Dr. Dixon has given me two or more bottles, and it has only been at the end of the experiment that I have been made acquainted with the exact nature of their contents.

My own work has been chiefly on caffeine and alcohol,

and with the former of these we were rapidly successful in disguising the taste. We used citrate of caffeine, and an indistinguishable control mixture was made of gentian and citric acid. With alcohol we had greater difficulty ; but the consideration of this may be deferred till I come to deal with the work on that substance.

I have not myself experimented with subcutaneous injections of any drug, but it is obvious that control injections are in such a case just as necessary as are control mixtures when the drug is given by the mouth.

Most of those who have written on the action of drugs on the capacity for work have not distinguished definitely between the action on the pure capacity for work in the unfatigued condition and the action on the process of fatigue, with which we have especially to do in these lectures. A complete distinction of this kind is, perhaps, impossible, for it is probable that the fatigue process comes into play from the first moment of beginning to work ; but, nevertheless, the distinction can be made in practice to a great extent, and I shall endeavour to make it, not only in the account of my own work, but also in that of the work of others, even when it has not been made by the authors themselves.

The method which I have adopted of recording sets of ergograms separated by intervals of rest is particularly adapted to bring out the distinction in question, and we shall see that there is evidence that the effect of a drug may be different at the beginning of a set of ergograms from that shown as the set is continued.