

THE EFFECT OF BENZEDRINE ON DEPRESSIVE STATES.

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DR. TÓMASSON'S interesting remarks on the therapeutic effect of adrenergic and cholinergic drugs lead me to mention some experiments with benzedrine recently carried out at the Maudsley Hospital. These experiments primarily originated from different considerations. They were part of more extensive investigations into the connection between mental phenomena and blood-pressure and its fluctuations. Benzedrine seemed to be suitable for experimental alterations of the blood-pressure because its effect on arterial tension lies between that of adrenaline and ephedrine with regard to rapidity and intensity of action. Experiments on normal persons demonstrated a peculiar stimulating and euphorizing effect of the drug. The experimental subjects were selected as normal in regard to blood-pressure. They included several cases of mild depression. These also showed either a slight elation, or at least a decrease of their depression after the administration of the drug. This result encouraged further experiments on depressives of various kinds. These were always carried out in the following way: Patients whose mental state was well known and who had been constant for a period with regard to their blood-pressure were given at first small, and later slowly increasing doses of the drug. There were intervals without medication in which the subjects received inert tablets of the same appearance and taste as the benzedrine. The blood-pressure was taken several times daily.

Regarding the subjective experiences, two main groups can be isolated, namely one in which the initial stage is a mild intoxication, with slight disturbance of consciousness which is generally compared with drunkenness, or is called dizziness or giddiness. This state wears off and changes into either the normal state or into another state which is experienced by the second group immediately, namely a mild elation with motor disinhibition. Reactions of the first type are sometimes experienced as disagreeable, and the persons react to this experience according to their constitution. Experimenting on patients one has to be prepared occasionally for a hysterical reaction. The patients describe the euphorizing effect, for instance, as follows: "I felt more cheerful, much brighter than usual. I felt more self-confident. I smiled for the first time since my admission."

It is most impressive when melancholic patients report that they feel just as in their normal days or that "the world seemed a bright place generally". One of my patients said—and his remarks are interesting with regard to what we know about the effect of alcohol: "I felt like after a double whisky, so full of energy and self-confidence. I mean, like after a double whisky in my normal time. When I tried whisky at the beginning of this illness (his seventh endogenous depression) I only felt more miserable."

Observations like these apparently point not only to an influence on the mood, but also to an effect on the psycho-motor retardation. One sees in normal persons that they move faster, work quicker when under the effect of the drug. The same is the case with depressives of milder type. In two stuporose or semi-stuporose melancholic patients we also saw some awakening of motor activity. Two questions arise from these findings, a more theoretical and a more practical one, namely:

- (1) The question of the mechanism of these changes, and—
- (2) The question of the duration of the effect.

With regard to the first question, attention was paid mainly to the role of the blood-pressure, according to the starting-point of these investigations, as has been described elsewhere.* Benzadrine influences the blood-pressure. It also influences mood and psychomotor activity as mentioned above. The correlation between these two effects is less than unity, that is to say, there is a proportion of cases which have changes in blood-pressure without measurable psychic changes and vice versa. This has already been discussed in previous communications. Some recent observations seem to point in the same direction. Several severe depressive cases exhibited some psychic improvement with a slight fall of blood-pressure after relatively small doses. The interpretation probably is that the drop in the blood-pressure due to the decrease of the psychic tension counterbalanced the slight rise due to the small dose of benzadrine. As yet sufficient observations have not been collected to explain how far these reactions depend on dosage, speed of absorption and starting level. Relatively small fluctuations need a most cautious interpretation, since one finds spontaneous fluctuations, always surprising by their intensity and apparent irregularity, whenever one controls blood-pressure over long enough periods†. All these observations lead to the conclusion that the fluctuations of blood-pressure neither produce the mental changes nor are produced by them. One can only assume that the susceptibility to benzadrine is similar in the apparatus responsible for these two functions. The relation is sufficiently close for the fluctuations of blood-pressure to be made use of as an indicator of the efficiency in experiments. The effect of benzadrine, in the dose used, on other organs innervated by the vegetative nervous system is practically none, so that there is no hint as to the mode of action. Sleep alone is regularly disturbed even by

* Peoples, S. A., and Guttman, E., *Lancet*, 1936, p. 1107.

† Schott, A., *Guy's Hospital Reports*, vol. lxxxvi, 1936.

small doses. Therefore one must consider whether disturbances of sleep function can explain the mental alterations. It would be premature to suggest hypotheses about this, but it may be mentioned that the disturbance of sleep in manic-depressive insanity is a very regular symptom, and that the illness has been compared with hibernation from the biological standpoint.

The euphorizing effect of benzedrine lasts generally only a few hours, the total effect, including the disturbance of sleep, not longer than 24 hours. Continuous administration of subliminal doses, i.e., of such amounts as have no noticeable effect on the blood-pressure, seems to be without therapeutic effect as far as our present experience goes. Doses which raise the blood-pressure considerably can be given for a longer period only with all precautions to a specially selected group of patients. Therefore it will take a considerable time until one will be able to collect sufficient material to judge the therapeutic results, and even then there will be all the difficulties which are connected with the general difficulties of prognosis outlined by Dr. Lewis.

The present significance of benzedrine in the therapy of manic-depressive insanity seems to me best formulated in an utterance of a younger colleague: "It is a relief to hear such a patient say he feels better, instead of hearing his usual daily complaints." Certainly such a change, though transient, benefits the patient. The more chronic the case, the more important is such a demonstration of a possibility of recovery for him. In rare cases it may be the interruption of a vicious circle. The state of disinhibition may facilitate the approach to the patient and may give the opportunity for psychotherapeutic influence, and this will be considered as the more efficient the more one values psychic factors in the origin of depressions of all kinds according to Dr. Lewis's conceptions brought forward in his previous papers on melancholia.*

* *Journ. Ment. Sci.*, vol. lxxx, pp. 1 and 277, January and April, 1934.

Discussion.

Dr. STRÖM-OLSEN said that he was in general agreement with the views of Dr. Hennelly as regards the efficacy of prolonged narcosis. He disagreed with him, however, on the question of dosage. He found it a mistake to adhere to a fixed dosage of 4 c.c.; many patients required more and tolerated the drug well, whilst others soon showed signs of idiosyncrasy. After all, the whole point of insulin administration would be missed if the dose of somnifaine were reduced to quantities which ordinarily would be quite safe. He had experienced the best results in cases showing affective disturbances, whether on a manic-depressive, schizophrenic, or neurotic basis. Cases showing agitation, anxiety and apprehensive depression did far better than those with retarded depression and autistic tendencies, and in obsessional neurosis the treatment had no beneficial effect.

As regards the interesting findings of Drs. Hennelly and Yates on the blood-calcium level during narcosis, he would like to say that he, too, had investigated the blood calcium before, during and after narcosis in three cases. He had noted a somewhat larger fall in the calcium level, up to 18 or 20% of that before treatment. In his cases the fall did not begin until the third or fourth day, but the rise to normal was rapid after the cessation of treatment. In view of Dr. Tomasson's significant findings in the variations of the blood electrolytes in manic-depressive psychosis, he thought more work was required on these lines in connection with prolonged narcosis. He would like to ask Dr. Tomasson three questions: Firstly, what were his views concerning the mechanism by which these changes in the electrolytes were brought about? Secondly, were they primary or secondary changes? And thirdly, did he think the changes in the calcium level during prolonged narcosis formed a mechanism partly responsible for the therapeutic effect?

Dr. G. W. T. H. FLEMING, referring to Dr. Parfitt's paper, said he thought enough care, possibly, was not taken in the matter of the induction of prolonged narcosis. Perhaps it was being rather lightly entered upon by some people. He himself came across an instance of a medical officer who pooh-poohed regular examination of the urine of patients who were undergoing this treatment, and the same man did not think glucose and insulin were necessary. It was surely dangerous for a medical officer to take that view. If medical officers essayed to tackle this treatment by prolonged narcosis without looking for toxic indications in the urine, they would quickly get into trouble. In prolonged narcosis insulin was given to avoid toxic symptoms; he believed he was right in saying it diminished the oxidation in the brain, and it was interesting that the exhibition of narcotics did the same; nevertheless insulin seemed to counteract the toxic effect of narcotics on the brain.

In reference to Dr. Tomasson's remarks, it had occurred to him, the speaker, that the quantity of calcium in the body seemed to have something to do with the symptoms; it might be a primary, or a secondary effect. Hæmatoporphyrin had been employed in manic-depressive cases, and it was said that it decreased the quantity of the blood calcium.

Therefore there were three different treatments, all doing exactly the same thing, and he, the speaker, thought there must be some disorder of the calcium metabolism in these cases.

He would like to know whether Dr. Tomasson and Dr. Hennelly had had experience of acetylcholine as a prophylactic in these cases.

Dr. A. A. W. PETRIE said that to some who saw prolonged narcosis carried out before the glucose and insulin modification was introduced the great objection was that of putting toxic substances into already toxic patients. A corollary to the administration of glucose and insulin which he had already seen was to give the glucose and insulin in toxic confusional cases, particularly where there was ketosis, and at times a considerable alleviation of the confusion occurred. Occasionally such ketosis and confusion might be associated with a manic-depressive

psychosis, and it was easier to deal with the other symptoms when the confusion had been dissipated.

The rationale of prolonged narcosis was a subject he felt sure everyone would like to discuss. In giving this treatment he felt that they were imitating nature. Everyone had seen cases pass into and remain in a profound stupor for a period before getting better. He agreed with Prof. Henderson that it was exceedingly difficult to differentiate the type of stupor, when it had reached a marked degree. While it was developing it was easy to label a case, say, of depressive stupor, but in any marked case it was often only possible from the history to get any real indication of the type of stupor which was under consideration. Cases passed from a state of agitation into stupor, the nature of which it was impossible to determine by direct observation. The period of quiescence during the stupor often provided the rest necessary for recuperation, and resulted in the improvement of the patient, and treatment by prolonged narcosis was merely imitating Nature in this respect.

Prof. Henderson had raised an interesting point regarding early cases, and symptoms arising between attacks. All engaged in the work had sought for drugs to allay anxiety and early depression. In the cyclothymic case, rest was obviously desirable. The speaker advised his patients to go to bed, and in some cases this extra rest seemed to abort the attack, but in a number of cases the cyclothymic tendency was too great, and one often wondered how far it was possible to alter or avert a recurrent phase in such a psychosis. Dr. A. J. Lewis had reminded us that hospital regime had taught such patients to adjust their habits more wisely. All engaged in the work of dealing with such patients were looking for drugs apart from bromides and hypnotics, and as previous speakers had indicated, acetylcholine and ephredine held out hopes.

He had only tried acetylcholine in cases of anxiety in too small a number to quote seriously. He had given it by mouth, and not by injection, which was difficult to arrange for out-patients. Suitable cases had been chosen, but the results obtained were poor. Although acetylcholine was theoretically indicated in suitable anxiety cases, the results were disappointing, and patients who had been on bromide asked to be put back on that drug.

With regard to ephredine, he had had an interesting case, a mildly depressed chronic anxiety neurotic, who had adjusted to this condition when he developed what was apparently idiopathic narcolepsy. Investigations for possible mid-brain lesions were made with negative results. As the patient was becoming incapacitated for his work by his frequently falling asleep, he was placed on doses of ephredine hydrochloride, gr. $\frac{1}{4}$ thrice daily, this just restored his balance, and he had since been able to carry on useful work, relapsing only when the drug was withheld. The development of such symptoms, super-imposed on an original anxiety state made the case of interest, and the exhibition of a drug calculated to stimulate the parasympathetic system, just enabled the patient to maintain equilibrium.

It was to be hoped that study of these drugs in early cases might enable successful treatment to be given in established cases.

Dr. H. A. PALMER said that his experience of continuous narcosis was very much on the same lines as those related by Dr. Parfitt, namely, that he thought that the improvement claimed for the insulin-glucose therapy must be taken into consideration with the fact that if the Cardiff workers were reducing their dosages to 4 c.c. a day, they were probably thereby eliminating the chief toxic effect. Nothing could be more striking than the fact that in Zurich, which could be regarded as the fountain-head of this treatment, they appeared to disregard this modification. If the glucose-insulin method was so striking in its results as the Cardiff people declared it to be, it was extraordinary that the Swiss workers had neglected it.

His own experience agreed with the Zurich dictum, that if one gave these patients plenty of fluid—five pints in the twenty-four hours—acetone would not often be

found in the urine. It was a surprise to him to hear it stated that 50% of cases had acetonuria.

Another point which required clearing up was the question of a specific barbiturate effect. Without entering into a discussion of the theories as to how the treatment acted, mental hospital officers sooner or later came to the belief—which they were willing to support by practical evidence—that there was some magic in the barbiturates over and above their sedative action. More research was needed. Fifty cases should be treated with such a drug as dial and fifty cases with paraldehyde, and the results compared. At Woodside Hospital they used a technique which was different from that adopted by the Cardiff workers: 2 c.c. of somnifaine was given twice a day under medical order; this was considered safe and fool-proof, though it must be admitted that there were cases in which, even after that dosage, trouble might arise. The nurse in charge of the case was given complete discretion—checked by the medical officer—to keep the patient asleep thereafter with paraldehyde in 1- or 2-drm. doses. At Zurich a mixture of barbiturate, paraldehyde and cardiac stimulants, marketed as “Cloettal”, was used, but he and his colleagues thought that, though a convenient homogeneous mixture, it confined the physician to a standard proportion of cortical and subcortical sedatives, and they preferred the method outlined above.

In these discussions he was surprised by the paucity of reference to the question of blood-pressure. He took it as a *sine qua non* that the nursing staff should have a stethoscope and should take the blood-pressure, in the same way as the temperature and the respiration were taken. Ephedrine and cardiazol not only restored blood-pressure, but also counteracted the sedative effect of the drug. Continental observers mostly favoured ephedrine. At Woodside they used cardiazol.

In no English article had he seen a reference to sleep charts. Unless some method of recording systematically the amount of sleep patients had was used, a discussion on continuous sleep could only proceed on casual lines. He thought all the sleep each patient had should be charted. At Woodside they had a chart for sleep which was filled up with as much care as if it were a temperature chart. The aim was to secure twenty hours of sleep for the patient in every twenty-four; anything less than sixteen hours they did not regard as continuous sleep.

There was also the question of breathing. In this respect he thought continental observers could safely be followed, namely, that one could never substitute biochemical methods for clinical observation; no testing of urine, or serological reaction, could be held to be a substitute for the judgment of a trained nurse. On the Continent emphasis was laid on the breathing, just as in the operating theatre: the surgeon and anaesthetist watched the patient's breathing and blood-pressure; they did not bother about testing the urine.

Another point of importance was the following: At Zurich they abolished all forms of oral feeding in this treatment; they gave no solid nourishment at all, as understood in this country. There were some who believed that the metabolic changes caused by starvation were beneficial to the patient. At Woodside it could be said that the staff were half-way in this respect; no solid food was given, but the fluid nourishment was given by the mouth. The reason for the Zurich regime was to avoid aspiration pneumonia, which was a cause of death.

A further point of interest was the psychotic phase of these cases. He did not like, in a scientific conference, to throw out suggestions which had not a scientific backing, but his impression was that the patients who were most mad seemed to do best. That was an empirical observation, which he had not submitted to experimental analysis.

Dr. A. E. HASLAM FOX mentioned two cases under somnifaine treatment who developed gangrene of the toes. He asked whether Dr. Hennelly had had any similar experience with his cases.

Dr. TOMASSON, in reply, thanked all who had taken part in the discussion. Two methods had been discussed: prolonged sleep and a prolongation of the waking

state. Acetylcholine treatment meant a prolonged state of sleeplessness. He had not heard of cases of psychosis through sleeplessness, therefore he did not think that sleeplessness as such was dangerous. Prolonged sleep, however, might be, in some cases, double-edged; and in cases in which it was known that patients would recover, whatever was done, it was necessary to be cautious and to avoid using double-edged weapons. Therefore he had not used prolonged narcosis for some years.

There was a further fundamental difference in the two methods. Acetylcholine treatment was based on the chemical and physiological alterations found in the patients. Only after this had been established had they been used. That seemed to be the most interesting thing about the acetylcholine and ephedrine treatment: the correction of definite somatic deviations seemed to be sufficient to cure the psychotic trouble.

He had no definite conception of the mechanism involved in the alterations of the electrolytes. As far as possible he had tried to avoid evolving any definite theory as to these things; he thought it was better to collect more facts before starting with a theory. On the other hand, after having seen the effect of the correction of the autonomic electrolytic alterations he had founded a theory of the manic-depressive psychoses, but that was not for discussion now. In a number of the cases which he had been able to follow through several weeks, he knew that during five, six, even seven days before an attack there were deviations in the electrolytes; whether the attack would be mania or melancholia he could not tell; he had not been able to detect changes in the patients during those days. But he had seen cases in which he had not been able to detect any preliminary alterations in the electrolytes. Hence he did not maintain any definite opinion on this.

Dr. Ström-Olsen had asked whether the fall in calcium after prolonged narcosis would be associated with acetylcholine treatment. The speaker thought there was a definite connecting link, but there would be no use in discussing it at present. Facts should be collected, and possible theories could be discussed privately.

Dr. Fleming had asked whether he, the speaker, had any experience of acetylcholine as a prophylactic. To that he would answer "Yes" and "No". In the more definite cases of manic-depressive psychosis he had not, but in the slighter cases, the out-patient cases of melancholia, he had had some experience with it; and in those cases he had found a diminution of parasympathetic tone alone.

With regard to recurrent mania, he had a case which came every three weeks, and had been on acetylcholine for two years. When his wife detected anything in his behaviour which she thought meant the onset of an attack, she gave the drug, and he had not had an attack for two years.

Dr. Petrie remarked that he had tried acetylcholine in cases of anxiety, but without effect. That accorded with his own experience; he had not seen any benefit in anxiety states as such.

He had not spoken of the depressions; they were more complicated than the manias, and he did not think they were so favourable for experiment. But there were sixteen depression cases in which there occurred a definite diminution of the sympathetic pulse, and in those cases no anxiety was present. Those cases reacted very well to ephedrine, though some of the cases would recover without treatment.

Dr. Parfitt's remarks had interested him a good deal. With reference to the cases of mania which lasted four to fourteen months, that seemed to be about the European average of mania, except for Russia, where, according to the information received from that country, it lasted longer.

Dr. HENNELLY, in reply, said it had been found in his institution, as a routine, that 4 c.c. of somnifaine in twenty-four hours, in a dark room, was sufficient to maintain sleep for sixteen to eighteen hours a day. If the circumstances warranted it and the patient was in good physical condition and there was no acetoneuria, he had no hesitation in giving 6 c.c. If further sedatives were needed, say in cases

of acute mania, 2 drms. of paraldehyde was given in addition. In any case, on account of its toxicity, not more than 6 c.c. of somnifaine was given in the twenty-four hours. Recognition of danger-signals and having nurses who were thoroughly familiar with the treatment was to him all-important. He and his colleagues had not used acetylcholine experimentally in manic-depressive psychosis. He did not think that reducing the dose of somnifaine to 4 c.c. daily was altogether responsible for the absence of dangerous symptoms, since even with the reduced dose acetoneuria occurred at some time or other in about 50% of cases. That was why he stressed daily morning examination of the urine. At Cardiff, Cloetta's mixture had been given a fair trial. There was a great deal of trouble associated with its administration. It had to be given per rectum, nothing whatever being given by the mouth during the narcosis, and nutrient enemata had to be given every three hours. For these reasons, and from the point of view of convenience for the nursing staff, its use was discontinued; they saw no advantage in making the work harder when no better results were achieved. The fall of blood-pressure, as mentioned in the paper, was always taken into account. There it was stated that a fall of more than 25 mm. of mercury was taken as a distinct danger-signal, and was evidence of the possibility of cardiac collapse if not checked. Breathing, similarly, was always carefully watched. In Cardiff sleep charts were always used, sleep being charted in the same way as were temperature and pulse. These charts enabled one to see at a glance the amount of sleep and the degree of wakefulness in the twenty-four hours. It was hoped to publish those charts at a later date. He did not agree with Dr. Palmer that most of the recorded deaths following this treatment were due to aspiration pneumonia.

In reply to Dr. Haslam Fox, over 300 patients had been treated with prolonged narcosis in Cardiff, and he had never seen among them gangrene as a complication; neither did he think it was mentioned in the literature.

Sir LAURENCE BROCK referred to the insulin shock treatment of schizophrenia being carried out in Vienna. At the request of the Board of Control Dr. Isabel Wilson had visited Vienna and Münsingen in Switzerland and studied the treatment and had prepared a report which would shortly be published. He hoped it would receive careful study, and that this method of treatment would receive a careful and prolonged test in this country.
