DINITROPHENOL IN DEMENTIA PRÆCOX *

BY

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OBSERVATIONS of the effect of dinitrophenol on patients with dementia præcox should prove of value in (1) determining the reaction of these patients to its therapeutic use, and (2) extending our knowledge of this new drug. Cutting, Mehrrens and Tainter,¹ and Tainter, Stockton and Cutting,² have reported their observations of the action of alphasdinitrophenol. Therapeutic doses cause an increase in metabolism, and with it a loss of weight without fever. The indifference and lack of spontaneity in dementia præcox, we thought, offer a rational basis for the use of a drug which stimulates metabolism. Hoskins and Walsh,³ among others, have reported that the rate of oxygen consumption in schizophrenic patients is below normal. During the progress of our work Masserman and Goldsmith⁴ reported their observations of the effects of dinitrophenol on 'eighteen patients whose psychobiologic status was characterized by sluggishness, passivity and apathy.' The mental changes in their patients had occurred within the previous year.

TECHNIQUE

Twelve female patients with dementia præcox of the hebephrenic type were selected for this investigation. They ranged in age from 19 to 63 years, and in weight from 135 to 197.5 lbs. All of them had been in the institution from two to 24 years, except two, who had been here six weeks and seven months respectively. All of the group except one refused to do any work. One of the patients was deteriorated to the point of being a 'soiler.' With the exception of one who is employed in industrial work, all were unco-operative in varying degrees at the beginning of the treatment. Co-operative-ness increased as the study progressed. Six were given a preliminary period of attention, with the hope of securing better co-operation. In this group we were able to get reasonably accurate oxygen consumption rates† on four before medication was started. Of the patients who had not received a preliminary period of attention, we obtained satisfactory readings on two. None of the patients suffered from any gross organic disease. Blood pressure,

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† We have adopted the term 'Oxygen Consumption Rate,' as proposed by Hoskins, to replace 'Basal Metabolic Rate.' We still use the standard notations of plus and minus.

pulse, temperature, respiration and weight were noted, prior to medication, daily during medication, and during the first few days after medication was discontinued.

No laboratory work was done on two of the patients, as it was thought that the increased attention incident to the frequent tests might be a factor in any mental improvement that might result. The patients had to be promised various rewards in order to gain their co-operation. Our conversation with the patients (previous to and during the various tests) might be a form of psychotherapy. Therefore, these two patients were not given any attention by us and served as controls for the effect of psychotherapy. The nurse administered the drug to them and also weighed them daily and took temperature readings.

Oxygen consumption rates were obtained prior to medication on ten patients. Blood chemistry studies and blood counts were made on six patients and urinalysis on four, before medication was started. Eight patients were given daily, in divided doses, 100 mg. (1.5 grains) of sodium dinitrophenol. The dose was gradually increased to 270 mg. per day. Four patients were started with 60 mg. alphadinitrophenol per day, which was gradually increased to 300 mg. The dosage was not increased to the maximum if the weight loss was rapid on a small dose. Only one patient was not placed on the maximum dosage because she lost weight rapidly on the initial dose. No change was made in the diet which the patients had previously received.

After medication was started, oxygen consumption rates, blood chemistry, including icteric index, cholesterol and blood counts were determined periodically on all patients except the two controls. In addition to daily notations of weight, blood pressure, temperature and pulse, daily observations were made of skin changes, perspiration, gastric distress, spontaneous complaints and mental status.

Seven of the patients were on treatment for 60 days and four for 30 days. Medication was discontinued in the case of one patient at the end of 32 days because the oxygen consumption rate had increased to plus 66. Blood chemistry studies were continued for several days after treatment was discontinued. Weights are still being recorded to determine the permanence of the weight reduction. Oxygen consumption rates were determined every two to four days after treatment until a normal reading was reached.

REACTIONS OF PATIENTS WITH DEMENTIA PRÆCOX TO DINITROPHENOL

The average oxygen consumption rate before treatment was 11.28. The average increase in the oxygen consumption after four weeks of treatment was 37.16. The range of increase was from 21 to 57. Two patients who had been on the maximum dosage (270 mg.) had not increased their oxygen

consumption nor had they lost any weight. Both of these patients had obvious endocrine dysfunction. They were obese, with a hypopituitary type of fat distribution, and had been diagnosed as cases of hypopituitarism. They had fat pads about the pelvis and shoulder girdles and none below the elbows and knees. The average oxygen consumption rate for the entire group two weeks after the completion of treatment was 6.5. This was somewhat lower than the pre-treatment rate, but the co-operation of the patients at this time was considerably better and they approached more nearly basal conditions. The pre-treatment determination was felt to be higher than the true rate. We felt that the oxygen consumption rates had returned to the pre-treatment values.

The average loss of weight per week for the group was 1.44 lbs. Two of the patients mentioned above, who had obvious endocrine dysfunction, had not lost any weight. The range of weight loss was from 2.50 to 0.7 lbs. per week. One patient lost a considerably greater amount (2.5 lbs. per week) than any of the others. This patient was the only one whose dose was not increased to the maximum. She lost weight rapidly on only 100 mg. sodium dinitrophenol daily.

The non-protein nitrogen of the blood was increased from the pre-treatment values on all patients. The average increase in non-protein nitrogen after four weeks of treatment was 2.66 mg. per 100 c.c. The range of increase was from 9.0 to 0.3 mg. In the patients who were on treatment for 60 days, the average increase from the fourth to the eighth week was 8.3 mg. The non-protein nitrogen had not returned to the lower pre-treatment values when determined two weeks after completion of treatment.

In the determination of the icteric index, the colour due to dinitrophenol, which is a dye closely related to picric acid, was removed with dilute hydrochloric acid. We found an average increase of 6.6 in the icteric index. Two weeks after the drug was discontinued the values decreased. The average decrease was 4.56. The Van den Bergh reactions on all patients were negative.

The blood cholesterol⁵ was lowered in all patients during treatment and was increased again after the drug was discontinued.

We observed no significant changes in pulse rate, blood pressure, temperature, respiration and cellular constituents of the blood. Urinalysis was consistently negative. One patient had a gastrointestinal disturbance. This patient showed the greatest mental improvement and her case is reported in detail below.

Mental Reactions.—One patient, whose case is reported, showed definite improvement in spontaneity, sociability and interest in work. Two patients improved in general behaviour, interest in personal appearance and in their tasks in the occupational therapy class. Two patients showed slight improvement. One of the patients who noticeably improved was a case of hypopituitarism and did not respond to dinitrophenol with any change in weight

or oxygen consumption rate. The two patients who had not received any attention with the administration of the drug, and thus served as controls for any incidental psychotherapy, did not show any change from their pre-treatment behaviour. The remaining four patients (three of whom were the oldest of the group) showed no change.

CASE REPORT

M.C., a single white girl, was admitted to Elgin State Hospital on March 2, 1934. She is the oldest of three siblings and had three years of high school. The family history is without significance. She was always quiet, had few friends, and rarely associated with the opposite sex. Fifteen months prior to admission she lost interest in school and preferred to stay in bed. She gradually became more and more careless of her appearance and lost interest in household tasks. She slept poorly and thought someone was coming through the wall to stab her. Several days prior to admission she became acutely disturbed, tore off all her clothing, fought with her mother, and tried to run out of the house in a nude condition. In the hospital she was found to be extremely indifferent and apathetic. When stimulated too much she became very irritable and unco-operative. She neglected her personal appearance, had no spontaneous speech, and rarely answered questions.

After six weeks of observation she was placed on dinitrophenol therapy and incidentally received considerable daily attention. Her weight at the beginning of treatment was 141 lbs. After one week she was co-operating fairly well for all tests, and after two weeks joined an occupational therapy class. But there was no significant change in her behaviour until at the end of the third week of treatment, when she began to show some spontaneity and took noticeable interest in the class work. She has maintained this improvement, with slight progress, as shown by increased sociability and requests for more difficult work in the occupational therapy department.

The laboratory findings in this case were as follows: Oxygen consumption rate prior to medication was plus 12. After treatment for two weeks it was plus 26; two weeks later, plus 33, and after 40 days it was plus 60. After this oxygen consumption rate was determined (60 in air), the patient was placed in a tub of cold water at 58° F. (as subject of another type of experiment). Her oxygen consumption rate in water was 68. Blood chemistry determinations prior to treatment were as follows: Icteric index, 7.5; cholesterol, 207.67 mg. per 100 c.c. of blood; non-protein nitrogen, 27.8 mg. per 100 c.c.; hæmoglobin, 95 per cent. After two weeks of treatment icteric index was 6.1; cholesterol, 146.1 mg.; non-protein nitrogen, 27.5; and blood sugar, 81.63. After four weeks of treatment icteric index was 16.6; Van den Bergh test negative; cholesterol, 117.5; non-protein nitrogen, 29.5; sugar, 86.2; and hæmoglobin 88 per cent. At the end of treatment icteric index was 13.3; Van den Bergh test negative; cholesterol, 119 mg.; non-protein nitrogen, 36 mg.; sugar, 67.4 mg. Two weeks after treatment was stopped, icteric index was 10; Van den Bergh test negative; cholesterol, 175 mg.; non-protein nitrogen, 29.1 mg.; sugar, 78.50 mg.; and hæmoglobin, 78 per cent. Urine examinations and blood counts made from time to time were normal. Her average loss of weight per week was 1.75 lbs.

At the end of the fourth week of treatment she had a gastrointestinal disturbance consisting of nausea and vomiting. She was given larger quantities of water and a mild cathartic. Symptoms disappeared in 24 hours. There was no change in her usual pulse, temperature, respiration, and blood pressure, which were, respectively, 81, 98.8, 20, and 106 systolic and 70 diastolic. No change was made in the medication.

COMMENT

In the interpretation of the reactions of dementia præcox patients to dinitrophenol, it seems to us that any variation in response from that previously published may be due to a difference in reaction to the drug of these patients from that of normal individuals. One can attribute a difference in reactions to the drug from those of normal individuals to the fact that dementia præcox patients differ from others not only in the mental sphere, but also in physical organization. The presence of a constitutional basic factor, anatomic, chemical, constitutional or glandular, has been reported by numerous authors.⁶ A difference in reactions may be due to an inefficient mechanism for homeostasis. The physicochemical reactions consisted of an increase in non-protein nitrogen and icteric index and a decrease in blood cholesterol. Although the icteric index and blood cholesterol showed a tendency to return to the pre-treatment values, the non-protein nitrogen remained increased (two weeks after completion of the treatment). The non-protein nitrogen values were, however, within normal limits.

Toxic effects to contraindicate the use of this drug were not observed. The previously reported toxic reactions were due to (1) excessive initial dosage,^{7, 8} and (2) allergic reactions.⁹ (See Addendum, p. 235.)

It is of great significance that two patients with obvious endocrine dysfunction (hypopituitarism) failed to respond to dinitrophenol with increased oxygen consumption or loss of weight. The reported action of the drug is that of direct stimulation of cellular metabolism.¹ We cannot explain the mechanism of the inhibition of the metabolic response in these two patients, and further work is necessary.

Included among the five patients who improved mentally was one of the endocrine cases who had not responded physiologically to the drug. Two patients who were not given any increased attention did not show improvement. This would suggest that the drug was not the agent that caused improvement, but rather that the increased attention served to stimulate these apathetic patients. It is still a question whether the reported sub-normal oxygen consumption rates³ are causative of or consecutive to the disease. Moreover, it is only by inference that one concludes that the metabolism of the rest of the body as well as that of the central nervous system is stimulated. The other phase of the problem is the availability of oxygen. With toxic doses the blood becomes anoxæmic.¹⁰ The reactions of patients with dementia præcox to the administration of dinitrophenol plus oxygen should be of interest. The use of these two agents as a therapeutic experiment in dementia præcox is also suggested by the reports¹¹ of short lucid intervals in patients with catatonic dementia præcox which follow the administration of oxygen, or a mixture of oxygen and carbon dioxide.

SUMMARY AND CONCLUSIONS

The mental and physical reactions to the administration of dinitrophenol in 12 patients with dementia præcox were observed. The average increase in oxygen consumption rate was 37.16. The average loss of weight was 1.44 lbs. per week. Two patients with a hypopituitary type of fat distribution did not respond to dinitrophenol with either a loss of weight or increased oxygen consumption. The oxygen consumption rates returned to the pre-treatment values after the administration of the drug was discontinued. The non-protein nitrogen and icteric index increased and blood cholesterol decreased during treatment. The icteric index and the cholesterol showed a tendency to return to pre-treatment values, but the non-protein nitrogen remained increased. Five patients improved mentally. The increased attention given the patients during treatment cannot be ruled out as having been the chief agent in causing the mental improvement. The reactions of dementia præcox patients to the administration of dinitrophenol together with oxygen should be studied.

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Addendum :—After this article had been prepared there appeared reports of cases of agranulocytosis following the administration of dinitrophenol. One of the cases terminated fatally. (Silver, S., 'A New Danger in Dinitrophenol Therapy,' *Jour. Amer. Med. Assoc.*, 1934, **103**, 1058).