

Use of Dinitrophenol in Nutritional Disorders*

A Critical Survey of Clinical Results†

MAURICE L. TAINTER, M.D., WINDSOR C. CUTTING, M.D., AND
A. B. STOCKTON, M.D.

*Associate Professor of Pharmacology; Resident in Medicine; and Instructor
in Therapeutics; Stanford University School of Medicine,
San Francisco, Calif.*

A LITTLE over a year ago, our first clinical report on dinitrophenol appeared in the *Journal of the American Medical Association*.¹ The interest in and enthusiasm for this product were so great that its widespread use has become a matter of some concern in public health. The total amount of the drug being used is astonishing. For instance, during the past year, the Stanford Clinics have supplied to physicians, or to patients on physicians' prescriptions, over 1,200,000 capsules of dinitrophenol of 0.1 gm. each. Since the usual daily dose is about 3 such capsules and the average duration of treatment about 3 months, this corresponds to 4,500 patients treated with the drug in a year. In addition, upward of 20 wholesale drug firms are marketing the compound, which suggests that a considerable population is being medicated. Probably at least 100,000 persons have been

treated with the drug in this country alone. But this is not all, for reports of its clinical use have also appeared in the medical press of Canada, Great Britain, France, Sweden, Italy, and Australia. Therefore, it appeared timely to summarize the accumulated knowledge of the clinical effects of this drug, and to assess the results critically, in order to determine, if possible, the present status of this new therapeutic agent.

HISTORY

We began to study the actions of alpha dinitrophenol 2-4 first in animals and then in patients, in 1931, being stimulated to do so by the animal experiments of Heymans,² who used a similar compound, namely, dinitronaphthol. Dinitrophenol was not new, since it had been known as a dye for about a hundred years, and as an industrial poison for 32 years.³ There was some interest in its toxicology during the war, due to poisoning in munitions factories. Fundamental investigations of the actions of the compound were made at that time by Magne, Mayer, and collaborators in France, although their studies were not published until 16 years

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later, *i.e.*, in 1932.⁴ Our experimental results⁵ and those of all other investigators are in essential agreement on the remarkable powers of dinitrophenol for augmenting oxidative metabolism by a direct action on the tissues or cells. Prior to our work, there was no indication in any of the published papers that this potent metabolic stimulant might be of any therapeutic usefulness. Therefore, when we first drew attention to the possibility of producing metabolic changes in man with small non-toxic doses of dinitrophenol, there was presented to the medical profession a new tool for use in metabolic disorders.

MEDICAL USES

It has been shown^{1, 6, 7, 34} that dinitrophenol can be used to keep the metabolism at an increased level for prolonged periods of time. An increase in the metabolic rate of about 50 per cent can be maintained in most patients without difficulty, by proper selection of dosage; in fact, greater increases have been repeatedly produced.

Rabinowitch and Fowler¹⁸ state that they have found difficulty in standardizing the oral dose because of individual variability. Examination of their data shows that, when the probable error of clinical metabolic readings is considered, the agreement is as good as could be expected. Variability in sensitivity to drugs of all kinds is a matter of common knowledge, so that, if perfectly reproducible changes were claimed, it would throw doubt on the validity of the observations. In contrast to Rabinowitch, Dunlop⁷ finds a reasonably good agreement between the metabolic stimulation and the size of the dose, which confirms our experience. However, in treating ambulatory patients⁶ it is desirable to proceed conservatively by starting with small doses and increasing them, if necessary, according to the degree of response elicited.

When the drug is taken in adequate

dosage, the increased metabolic activity burns extra fat and carbohydrate and thereby reduces body weight.⁶ It is very interesting that the protein does not seem to be appreciably affected in the combustion process, as indicated by nitrogen excretion. Accordingly, the tissue framework tends to be conserved.^{7, 8, 14} In a preliminary report on the loss of body weight in obese individuals,⁶ it was stated that losses of 2 to 3 pounds a week could be obtained with doses of dinitrophenol which were well tolerated. Three other groups of workers have confirmed this result in smaller groups of patients,^{7, 9, 10} and it is now a common experience with many practising physicians.

Dunlop⁷ compared the relative efficiency of thyroid and dinitrophenol in reducing weight in a few selected patients. He found that thyroid upset the water balance of the body in such a way as to cause at once a rapid loss of weight by dehydration. On the other hand, dinitrophenol reduced the weight less rapidly, but in proportion to the metabolic increase and not by an effect on water balance. His experimental results do not satisfactorily establish his conclusion that "even in maximum therapeutic doses it (dinitrophenol) does not compare, as a weight reducer, with thyroid"; since he used both drugs for only a few days at a time, and during these periods the weight changes were so small as to be readily accounted for by shifts in the water balance.

The amount of permanent weight change that can be produced by dehydration in non-edematous patients is not great enough to be important where any significant amount of weight is to be lost. If this were not the case, simple dehydration procedures would answer the needs of this difficult clinical problem. Therefore, it appears to us that, before the therapeutic efficiencies of these drugs may be satisfactorily

compared, it is necessary to make observations over long periods of time, during which more than a few pounds are lost. It has been indicated by us in several publications^{11, 12} that dinitrophenol cannot be used to replace thyroid secretion. It is therefore misleading to compare the intensities of their actions since they act so differently qualitatively.

Since dinitrophenol can increase the tissue metabolism by a direct action on the cells, without producing the side-actions which accompany metabolic stimulation by thyroid, it offers, theoretically at least, interesting possible applications in medicine, besides its use in obesity. For instance, there have been reported interesting effects in psychiatric conditions,^{13, 14} and failure to relieve myxedema,^{7, 18} and many other studies are in progress. Because of its widespread and probably sometimes indiscriminate use by large numbers of people, it is pertinent to consider possible harmful effects from the compound.

FATAL EFFECTS

In experimental animals, a large enough dose of dinitrophenol will stimulate the heat production to the point where fatal fever results. The heat production may be increased 1,200 per cent, the body temperature increasing 0.2° C. per minute. Under these conditions, death is caused by heat rigor, that is, by heat-coagulation of tissues. Exactly similar effects can be produced in man provided a large enough dose is taken. This was seen occasionally in munition workers during the World War, who absorbed large amounts of dinitrophenol through the lungs or skin.

The first case of fatal poisoning from the therapeutic use of the drug was that of a physician who took a tremendous dose on two separate occasions, with the alleged object of treating an

imaginary syphilitic infection.¹⁵ In his second administration, he took 5 gm. of the drug as a single dose, which is a 17 day supply for most patients. A fatal fever resulted, with death in 12 hours.

The second death was a girl who bought the drug on her own responsibility from a druggist. On the fourth day of medication, she took 0.8 gm., which caused a fatal pyrexia.¹⁶ Since the daily dose during the first week or two should be only 0.1 gm.,⁶ it is obvious that this girl took a very excessive dose. In fact, it was a larger dose than we have ever used therapeutically, even after months of continuous medication.

The third death occurred in a psychiatric patient who was receiving doses within the therapeutic range.¹³ The clinical history of this patient's illness and death is completely at variance with the known actions of dinitrophenol, since there was a protracted course of illness and an absence of serious fever. Also, the autopsy and clinical studies were so incomplete as to preclude a correct diagnosis of the cause of death.

These three cases represent the reported fatalities from dinitrophenol. If the third case be excluded because of the question as to the true cause of the death, it is seen that neither of the other two cases was due to the use of the drug in the usual therapeutic doses. When one considers that some one hundred thousand patients have been treated with this exceedingly potent therapeutic agent, it is a matter of some gratification to know that fatalities have not been more numerous. It might be added in this connection that fatalities from the fever of dinitrophenol can be largely prevented, in animals at least, by chilling the skin with ice packs and by giving oxygen inhalations.¹⁷

There are also a number of observed, or theoretically possible, deleterious actions, which do not result fatally. These may be discussed according to the

organs involved, *i.e.*, skin, liver, kidneys, circulation, and gastrointestinal tract.

SKIN REACTIONS

In a series of 113 obese individuals,⁶ we observed the presence of skin rashes in about 7 per cent of cases. The rashes consisted of maculo-papular dermatitis, urticaria, or angio-neurotic-like swellings of the skin, accompanied by pruritus and occasionally by desquamation. There was usually a prodrome of itching before the skin lesions developed. Four similar cases have been reported to date,^{9, 19, 20, 21} and many more than these have undoubtedly occurred. Dintenfass²² has recorded still another case in which the dermatitis was associated with congestion of the middle ear.

The inference might possibly be drawn from certain reports that a Derrien reaction with the urine could be used as a means of predicting possible lack of tolerance to the drug. This idea rests on a misunderstanding of the nature of the test; it is merely the well known diazo reaction, which is positive in the presence of amino-nitrophenols. Hence, it only indicates that dinitrophenol has been absorbed in the body and has appeared in the urine in a reduced form. During the war, this reaction was used solely as a means of identifying those workers whose exposure resulted in appreciable absorption of the drug.²³ Bolliger has recently cast doubt on the value of the reaction for even this purpose.²⁴

Another possible way of predicting dermal intolerance is by the usual allergic skin tests. Frumess²⁰ states that, in a case of urticaria, he was able to reproduce the skin-sensitivity by passive transfer. However, an extensive series of skin tests²⁵ in patients with and without skin rashes, who received dinitrophenol therapeutically, has failed to bring out any evidence that skin-

sensitivity can be detected by patch, scratch, or intradermal wheal tests. Passive transfer tests were also negative. These methods would therefore seem unpromising as means of selecting patients for dinitrophenol medication.

Since the skin rashes may be very unpleasant or alarming in some cases, they constitute the main disadvantage in the therapeutic use of dinitrophenol. A saving feature, however, is that about half the patients who have had one skin reaction are able, after a short interval, to resume the medication without further difficulty.

LIVER DAMAGE

Much has been made by some editorial writers and clinical reporters of the possibility that dinitrophenol might damage the liver. This has been based mainly on reasoning by analogy from picric acid and other compounds. Since the dinitrophenol has a yellow color, which imparts an icteric tint to the blood plasma, it may be mistaken for the bile pigments of jaundice.²⁶ The differentiation from the latter may be readily made by adding dilute hydrochloric acid to the plasma which decolorizes the dye. In one patient suspected of liver injury, Rabinowitch¹⁸ found only a slight increase in the bilirubin in the blood and no change in the urobilinogen. At the next examination of this patient, the findings were all negative. Another case where liver injury was apparently produced has been recently reported by Sidel.³⁴

We have seen no evidences of damage to the liver in our clinical cases,⁶ and at this time we may add more extensive data on this question. In 17 patients who were given an average of 0.3 gm. of sodium dinitrophenol daily for from 1 to 5 months, there were made 22 determinations of the icteric indices of their acidified blood plasmas. The average value was 8.2 units with a range of from 4.8 to 16.3. Fourteen

determinations on non-medicated patients gave an average index of 7.6, with a range of from 4.2 to 10.0. In 45 patients, the bilirubin content of the blood serum was determined by the van den Bergh reaction.* This group of patients received an average daily dose of 0.3 gm. (range 0.1 to 0.6 gm.) for an average period of 19 weeks (range 2 to 50 weeks). The average total amount of the drug taken was 36 gm., with a range of from 2.8 to 122.5 gm. In these patients, the bilirubin averaged 0.29 units, with a range of from 0.13 to 0.79 units. Only 2 patients of the 45 showed values over 0.5, but these had no demonstrable clinical evidence of liver disturbance.

If the dinitrophenol injured the liver progressively, it might be expected that the bilirubin of the blood would increase with the total amount of the drug taken. The following tabulation shows that no such increase was present, which further supports the conclusion that damage to the liver was not produced in these patients.

<i>Average total amount of dinitrophenol taken in gm.</i>	<i>Number of cases</i>	<i>Bilirubin units (average)</i>
0 - 10.0	12	0.27
10.1- 30.0	8	0.34
30.1- 40.0	14	0.32
40.1- 80.0	8	0.22
80.1-122.5	4	0.31

The van den Bergh reaction was repeated in 6 patients some time after stoppage of the dinitrophenol medication. These patients had been off the drug for an average of 36 weeks when they showed an average bilirubin content of 0.24 units (range 0.15 to 0.40). Accordingly, there was no evidence of delayed liver damage.

It has been observed by us¹⁵ and by Poole and Haining¹⁶ that, in fatal dinitrophenol poisoning, destructive

changes may occur in the liver as well as in other viscera. It must be remembered that death in these cases was accompanied by a very high fever, which in itself is enough to account for the morphological changes observed in the liver cells. The usual therapeutic doses of the drug produce no change in body temperature and also no evidences of change in liver function. However, the possibility must still be left open that in occasional patients an idiosyncrasy may exist which might mediate damages to the liver.

KIDNEY

If dinitrophenol in therapeutic doses damaged the kidneys, this would be manifested by albuminuria and related changes. Such evidences could scarcely go undiscovered, since urinalysis is such a common routine procedure. Hence, it becomes of significance that only 1 possible case of renal injury has been reported thus far. Rabinowitch and Fowler¹⁸ reported 1 patient who developed an albuminuria and high blood urea during dinitrophenol medication. Three weeks later, the urine, and the blood urea and creatinine were all normal. In our patients⁶ albuminuria has never been produced by the drug, but on the contrary a limited number of patients have lost their preëxisting albuminurias during the medication. Our experimental studies^{27, 30} on animals have also shown the drug to be quite devoid of toxic effects on the kidneys. Therefore, the possibility of renal damage would appear so remote as to cause little or no concern in the therapeutic use of the drug.

CIRCULATION

One of the most striking features of the metabolic stimulation of dinitrophenol is a lack of significant changes in blood pressure or pulse rate, unless therapeutic doses are exceeded.^{1, 6} That is, the metabolism may be increased by

* The van den Bergh data were obtained with the assistance of Elizabeth Hines.

as much as 50 per cent without demonstrable changes in circulatory activity. This phenomenon is in striking contrast to the effects of thyroid administration, where circulatory changes are a marked feature of the symptom-complex. Confirmation of this early finding has been given by Looney and Hoskins,¹⁴ Rabinowitch,¹⁸ and Dunlop,⁷ and more recently again by ourselves working under different conditions.²⁸ We have observed that, when a patient feels very hot and flushed, there is a rise in venous pressure. This may be the result of vasodilatation in the skin rather than the metabolic stimulation, since the venous pressure changes do not correlate with those of metabolism. Rosenblum³⁵ observed in patients whose metabolic rates were increased 37 per cent by dinitrophenol, that the circulation time from the arm to the tongue was unchanged. This would be in keeping with the lack of changes in the blood pressure and pulse rate previously reported.

Masserman and Goldsmith¹³ have made the rather startling claim that 5 out of their 18 psychiatric patients showed toxic effects characterized by a fall of blood pressure, tachycardia, stupor, etc. No such effects were observed by Looney and Hoskins¹⁴ in a similar group of patients, nor in upward of 300 non-psychotic patients observed by us. Not a single case of hypotension has been observed by, or reported to, us and none has been reported in the literature. The unconfirmed and possibly misinterpreted observations of circulatory changes by Masserman and Goldsmith, taken together with an unexplained death among their patients, suggests that there may have been some error in the therapeutic procedures they used, such as the possible use of a wrong isomer or an impure preparation of dinitrophenol.

Patients who have hypertension can be medicated with dinitrophenol like

other patients. As they lose weight, the hypertension is usually improved⁶ and the associated symptoms are ameliorated.

BLOOD

In studying the possibility that dinitrophenol might affect the blood, both the red and white corpuscles must be considered. Thus far we have not made extensive red cell counts in patients receiving dinitrophenol, but there have been no evidences of anemia, even after months of medication. The oxygen capacity of the blood of 15 patients was determined for possible evidences of injury to the respiratory function of the blood. Since the normal oxygen capacity of the blood varies from 18 to 21 vols. per cent and in these medicated patients the average value was 19.5 vols. per cent with a range of from 18 to 22 per cent, there is no reason to believe that the blood was injured. These patients received an average of 0.3 gm. sodium dinitrophenol daily, for an average period of 6 weeks. The addition of sodium dinitrophenol, in concentrated solution to several specimens of blood did not change the oxygen capacity. Therefore, the drug does not appear to affect the hemoglobin of the blood *in vitro* and *in vivo*.

Study was also made of the fragility of the red cells of these same patients to determine whether there was any increased tendency of the cells to hemolyze. The cells were exposed to various strengths of hypotonic salt solution and the concentrations at which hemolysis began and was complete were noted.²⁹ Hemolysis of normal cells begins at from 0.46 to 0.38 per cent concentration and is complete at from 0.34 to 0.25 per cent. With the cells of the medicated patients, the hemolysis began at an average of 0.44 per cent, with a range of from 0.42 to 0.46 per cent, and was complete at an average of

0.31 per cent, with a range from 0.25 to 0.38 per cent. Since these values were all within the normal range, there was no evidence of alteration in fragility of the red cells.

Current emphasis on the problem of agranulocytosis makes it desirable to observe the white blood cells in patients receiving dinitrophenol. We have seen no cases of malignant neutropenia, or of any condition which might be ascribed to a reduction in the number of white blood cells, among the considerable number of patients treated at Stanford. In addition, we have examined the blood and bone marrow of dogs given extra-therapeutic doses of dinitrophenol daily for 6 months without finding any abnormalities.³⁰ However, Hoffman, Butt, and Hickey³¹ have reported 1 patient who developed a neutropenia while taking dinitrophenol, and who recovered. A second case has recently been reported,³⁶ and other unpublished cases have apparently occurred.³³ Agranulocytosis has been reported in association with medication with a large number of unrelated drugs, and even in the absence of medication. Although the cause of agranulocytosis is not yet understood, it is probable that the underlying factor common to all cases is a defective bone-marrow which requires some, and apparently sometimes a relatively insignificant, exciting cause to precipitate the crisis. Given such bone-marrow, it is conceivable that many extraneous agents, physical, bacterial or chemical, and including even dinitrophenol, might initiate the clinical syndrome. The fact is that the vast majority of patients can take massive doses of the various drugs alleged to cause agranulocytosis without damage to white cells, and yet in a sensitive individual even a small therapeutic dose of one of these drugs may suffice to precipitate the condition. However this may be, we shall continue to examine all patients receiving dinitrophenol with

the possibility of agranulocytosis in mind, and hope to present more specific data on the question at some future time.

GASTROINTESTINAL TRACT

Heymans has stated that dinitrophenol causes very severe gastroenteritis and loss of appetite, and suggested that the loss of weight was due to the failure or inability of the patient to eat.³² In our very large series of patients, there have been only 3 cases with digestive complaints during the medication with dinitrophenol. These complaints lasted only for a few days, such as might be expected from a slight dietary indiscretion. The claim that this drug is a severe irritant to the gastrointestinal tract of patients is unwarranted for doses of therapeutic range, according to our experience and to that of large numbers of physicians prescribing it. Tissues from the gastrointestinal tracts of dogs given the drug for 6 months by mouth also showed no evidences of abnormal changes.³⁰ Therefore, there is no good reason for postulating a hypothetical gastroenteritis as the cause of the loss of body weight in the face of repeatedly demonstrated metabolic stimulation which does adequately account for it.

DISCUSSION AND SUMMARY

It can now be said that dinitrophenol is of definite value as a drug for treating obesity and perhaps some other metabolic disorders. In the hands of the medical profession, it can be used with the maximum benefit and with minimum deleterious results. Unfortunately, its sale cannot be confined to physicians under present legal regulations. As a result, it can be, and is being, sold in patent and proprietary medicines under names which do not reveal its presence. A person buying such an anti-fat remedy over the drug store counter, with no more directions

as to its use, or warning of possible harmful effects, than the manufacturer pleases to put on the label, may run a serious danger of doing himself harm. This problem is particularly pressing since "obesity cures" are extensively bought by fat people for self-medication without diagnosis. Therefore, it would seem desirable that dinitrophenol be added to the poison list, and its sale regulated so it could not be obtained except on a physician's prescription.

In the first enthusiasm for a new drug, which has spectacular actions, it is to be expected that it may be used somewhat too freely. This we have consistently tried to prevent in the case of dinitrophenol by stressing the potential dangers of the compound when used indiscriminately. Certainly, it should not be used as a routine measure in any clinical condition. Obesity can be controlled in most cases by the physician who will patiently supervise the dietary regime. In other cases, thyroid or thyroxine may be needed. It is only when all other measures have been thoroughly tried and found ineffective, and when there is impelling need for weight reduction, that dinitrophenol medication, with a knowledge of attending risks, should be undertaken. Under these circumstances, the physician must balance the prospective benefit against the potential harm, just as he does with any therapeutic procedure, and give the patient his best chance.

This summary of the clinical effects and side actions of dinitrophenol shows that in some respects this drug is not ideal as a therapeutic agent, since it may cause certain undesired side-actions in a portion of the patients treated. However, this does not mean that it cannot be used safely under proper conditions. Investigations are under way in our own and many other laboratories to develop new compounds which may be better than this original or parent substance. It would be only a matter of chance, if

dinitrophenol happened to be better than any substitute that could subsequently be prepared. Therefore, it may be expected that the next few years will see other compounds brought forward and advocated. Perhaps some one of them may supplant alpha dinitrophenol as the agent of choice. However, this will in no way affect the great significance of dinitrophenol as having been the first foreign agent, or drug, to be demonstrated as a very potent and well nigh universal metabolic stimulant, which was available for experimental purposes and useful for alleviation of human infirmity.

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