Biological Study of Dinitro Drugs in Humans

By Dr. Jacques Bell

Bell, Jacques. 1939. Etude biologique des produits dinitres chez l'homme. Medecine. 19:749-54.

There is a fundamental difference between biological experimentation with dinitrophenol in humans and what was done in the laboratories of physiologists. These last are essentially interested in hyperthermia (Andre Mayer, Leon Binet, etc.). Yet, in medicine, the doses of dinitrophenol employed do not determine any elevation of temperature. The physiological effects, observed in these conditions, differ considerably from those made by the experimenter. It is thus for example that the animal in hyperthermia presents a polypnoea [rapid, shallow breathing], a hyperglycemia, a hypoglobulinemia that one does not observe with therapeutic doses; it is because experimental hyperthermia is essentially a combustion of carbohydrates, while therapeutic hypermetabolism is mainly a combustion of lipids, as is shown by the lowering of respiratory quotient.

One shouldn't be surprised at these differences. The clinician uses strychnine as a tonic; the experimenter employs it to cause convulsions. The clinician uses adrenaline, at titrated doses, to produce a manageable hypertension; the physiologist, with massive doses causes acute edema of the lung.

Yet, to base the clinical use of adrenaline or of strychnine on acute edema of the lung or experimental convulsions, constitutes an obvious error. It is the same for dinitrophenol.

In France, besides, one uses almost exclusively dinitrophenyl-lysidine, which, according to the same terms of the study made by Professor Pouchet, "is easy to purify by crystallization, to easily modify the first of its components from the point of view of toxicity, dissolves easily in water, and, by addition of the methylglyoxalidine (lysidine) group, favors energetically the elimination of waste."

After Professor Pouchet, we have, in our thesis [1], demonstrated the superiority of this last product; in what follows, it is by comparison with him that we will study the biology of the dinitro drugs.

We shall see, in order:

I. Their action on the basal metabolism,
II. Their visceral action,
III. Their nutritional action.

I. ACTION ON BASAL METABOLISM

After the experimental research of Magne, Mayer and Plantefol, in animals, the experiments of Cutting and Tainter has confirmed, in humans, that dinitrophenol is a drug which strongly increases the metabolism, exaggerating the oxidation process of the organism by direct action on the cellular metabolism. These authors have observed a rise of close to 20% after one hour, being able to attain 70% in ten hours and a tendency to return to normal at 24 hours if the administration of the medicine is not continued.

This increase is not due to a sympathetic deregulation. The dinitro treatment respects the autonomic nervous system, in an inverse way from thyroxine, which, at slimming doses, determines rapidly some tremors, insomnia, and a mental instability of the type "basedowien." [a thyroid illness where one secretes too much thyroid hormones]

In the thyroid illnesses, or the thyroid treatments, there is an inverse connection between the level of the basal metabolism and that of blood cholesterol, this being as much lower as the metabolism is higher. One doesn't observe similar phenomena in the course of dinitro treatment.

This fact indicates that the changes caused in the blood cholesterol in the course of thyroid treatment are directly linked with the thyroid medication and not at all to do with the elevation of the metabolism which is responsible for the reduction of obesity. Dinitrophenol has almost no action on the blood cholesterol. (Grant and Schube).

An attentive exploration of the nutritional changes in the course of dinitro treatment, in the cases of five obese women, has shown the following facts:

1. The administration of dinitrophenol, at a dose of 3.5 mg per kilo, increases the total production of heat by about 40%, from the 3rd or 4th day.

2. This increase of the metabolism is due mostly to an increase in the combustion of the fat and a little to combustion of carbohydrates.

3. Dinitrophenol does not attack cell tissue albumin and does not determine the fat loss to the expense of the muscles, contrary to thyroxine.

II. VISCERAL ACTION

Dinitro treatment respects the liver, the kidneys, the cardio-vascular system and the blood.

This innocuity for the principal visceral functions is without doubt one of the main reasons for the distribution of this therapy.

Tainter, Stockton and Cutting have reported a series of cases in which one had measured the plasma bile index and determined the test of Van de Bergh. Their analyses demonstrate, beyond a doubt, that the liver does not suffer any damage in the course of dinitro treatment.

Experimental studies on animals do not show toxic effects of dinitrophenol on the kidney (Taitner, Cutting, Wood and Proescher). Anatomical-pathological examinations of animals, even those which died from a massive dose of dinitrophenol, do not reveal any important anatomical changes, except a small degree of cytolysis. Clinical documents are not abundant, but, on the whole, do not seem to demonstrate that dinitrophenol is toxic for the kidneys.

As T.L. Schulte and M.L. Tainter wrote, "it doesn't seem that dinitrophenol at usual clinical doses is likely to harm the kidneys."

Dinitrophenol is remarkable for its absence of effect on the cardio-vascular system. Even when the basal metabolism is found elevated to significant levels, there is no change in the rhythm of the pulse (Rosenblum).

On this point, dinitrophenol differs from all the other metabolic accelerants known. It is an observation that all the clinicians, today, have had occasion to make.

All the clinicians know that, contrary to thyroxine, dinitrophenol is absolutely devoid of toxicity for the heart.

The research of Professor Loeper and of his students has demonstrated the physiological and clinical importance of myocardiac glycogen. Extensive studies by P.N. Taussig have shown that dinitrophenol does not reduce cardiac glycogen at all and that, on this point, it differs completely from thyroxine.

III. ACTION ON NUTRITION

The influence of dinitro therapy on nutrition has been the object of a very important clinical study.

"One does not observe variations in the elimination of chlorine; eliminated phosphorus varies sometimes more, sometimes less, the elimination of sulphur increases slightly, especially in the form of sulphur conjugates, urines show a small increase of total nitrogen and of urea." (Prof. Pouchet).

It is a well known fact that the administration of thyroid extract or hyperthyroidism is accompanied by an increased secretion of calcium and of phosphorus. This calcium and phosphorus in the urine are not due to the acceleration of metabolism, as one does not observe these facts either during fever, nor in the course of leukemias which raise the metabolism (J.C. Aub, N.B. Bauer, C.I. Heath, Alright, Bauer and Aub).

Thyroxine reduces bone density.

With dinitrophenol, nothing of the sort is observed. The experiments of Clarence L. Robbins show that dinitrophenol, in spite of the elevation of the metabolism that it produces, does not cause any increase of the loss of calcium or of phosphorus. An increase of 37% in the basal metabolism, caused by the ingestion of dinitrophenol, does not lead to modification in the excretion of these elements.

In normal individuals, when one administers dinitrophenol during a short period, it produces a small elevation of reduced substances in the blood after fasting (although one would not be able to call this hyperglycemia). When one administers the medication over a longer period, this phenomenon is not produced and there is a marked elevation of the tolerance to carbohydrates.

In diabetics, following treatments of short duration, the results are variable, the tolerance to glucose being as often increased as it is decreased, with parallel changes in the fasting blood sugar level. But, in prolonging the administration of the medication, one observes an increase of the tolerance of carbohydrates. Anyway, in basing himself on the study of 32 cases of diabetes, Simkins concludes that dinitrophenol is not toxic for diabetics. He remarks that this observation goes counter to some assertions that have been a little prematurely advanced.

Dinitrophenyl-lysidine at therapeutic doses therefore has an action on the organism which is completely physiological. This action has been demonstrated in obesity where it has been compared to the actions of thyroid medication and physical exercise.

The existence of obesities of glandular origin, especially by thyroid insufficiency, has resulted in the use of thyroxine in numerous subjects.

"This wasn't without inconveniences, sometimes grave, characterized especially by cardiac and nervous troubles; the effective dose of thyroxine is, in fact, very close to the toxic dose. Further, we has frequently seen these accidents persisting after the administration even of a single dose, which leads to the impossibility of stopping them immediately by a simple suspension of the medication. Yet, from the point of view of its specific action on the basal metabolism, dinitrophenol offers this precious advantage that the cessation of its use at the slightest appearance of signs indicating an imminence of intoxication results immediately in the arrest of those symptoms." (Professor Pouchet).

Finally, thyroxine causes a nitrogen malnutrition: it burns the muscle and fatigues the heart. Dinitrophenol-lysidine, to the contrary, causes a lipid-glycemic loss: it is the elimination of reserve materials without attacking visceral and muscle tissue.

As for physical exercise, it seems to act exactly like dinitro therapy. Marcowitz, in his communication to the Academy of Medicine of Toronto on October 9, 1934, based on 90 cases of obesity, having followed this treatment during a period of 16 months, concludes that its action may be succinctly described in saying that the effects on the organism are similar to those of physical exercises.

The fact is besides established by physiologists, since dinitrophenol raises thermogenesis and not the metabolic quotient.

All the clinicians know actually that dinitro medication is irreplaceable in cases of monstrous obesities which prevent all exercise. It can be used in the obese for whom occupations, life style or cardiac troubles do not permit physical exercises. It is indispensible for the grossly obese in cases of abdominal operations and immobilization due to illness (inflammation of fallopian tubes, appendicitis, etc.) for which there is an urgency to obtain a reduction of subcutaneous fat.

But this clinical use has not been able to be extended other than when the experimental research pursued on humans, with a dinitro drug free from impurities, has been able to demonstrate the biological effects of it in a very precise way.

1. La Therapeutique dinitree (J.-B. Bailliere et Fils, editeurs, 1937).

[no other bibliography]