

## FROM DISULFIRAM TO ANTABUSE: THE INVENTION OF A DRUG

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### Introduction

Antabuse® is the trade name for an organic sulfur compound, chemically identical to disulfiram or tetraethylthiuram disulfide, a light-gray crystalline powder with a molecular weight of 296.54. In 1945 Danish researchers observed that the substance caused very unpleasant physiological effects in persons who had consumed alcohol. A few years later this chance observation was turned into a profitable production of pills used to combat alcoholism (antabuse = anti-abuse). The new drug quickly came into general use in Denmark and also, if somewhat later and on a lesser scale, internationally.

While the literature on the biochemical and medical aspects of antabuse or disulfiram is massive (1), almost nothing has been written about its discovery and subsequent history. This paper focuses on the innovative phase in the period between 1945 and the early 1950s. How was the peculiar effect of disulfiram discovered? How was it turned into a marketable drug? What were the early clinical experiences?

To the extent that the discovery story of antabuse is known, it is probably because it is a typical case of serendipity, an unintended discovery made in a research process with a different goal (2). Most Americans would first have known of the new drug from an article titled "Drug for Drunks" in *Time* of December 6, 1948. "The discovery was an accident," according to the article, and the writer continued (3):

Copenhagen's Dr. Erik Jacobsen, 45, likes to try out new drugs on himself before giving them to his patients. One night before going to a dinner party he swallowed a couple of pills made of tetraethylthiuram-disulfide; they were supposed to be good for intestinal worms. To his surprise, Dr. Jacobsen found that any form of alcohol revolted him. When he sipped even a small glass of beer, his face got red, his heart started to pound, and he had trouble getting his breath.

Other accounts of this example of self-experimentation are more dramatic if not necessarily more authentic. Thus, according to a recent book, at one point, "Jacobsen's blood pressure fell to almost zero and he came close to death" (4). This incident happened after Jacobsen had taken a pill of disulfiram and subsequently had alcohol injected intravenously.

### Disulfiram before 1945

Whereas antabuse dates from 1948, disulfiram goes farther back in history. A Berlin chemist, M. Grodzki, reported in 1881 that he had synthesized a new compound from thiocarbamide and that its stoichiometric formula was  $C_{10}H_{20}N_2S_4$  (5). His report, published in *Berichte*, caused little attention. This was the heyday of organic synthesis, when chemists—and German chemists in particular—produced one new compound after the other. Grodzki's seemed to be just one more.

However, some twenty years later, disulfiram was introduced in the developing rubber industry to accelerate the vulcanization of rubber (6). The substance proved effective and was widely used in the vulcanization of both natural rubber and synthetic rubber products such as neoprene. It was in connection with the rubber industry that a possible connection between disulfiram and the ingestion of alcohol was first noticed. In 1937 E. E. Williams, a plant physician in the American rubber industry, described how workers in the plant, processing tetramethylthiuram monosulfide and disulfide, suffered trouble when ingesting alcohol (7). Williams thought that the adverse properties of disulfiram and related compounds to alcohol might perhaps lead to "the cure for alcoholism," but neither he nor others followed up the suggestion. The effect of disulfiram on intake of alcohol was also known in the Swedish rubber boot industry, without any one in Sweden suggesting its possible use as a drug against alcoholism (8).

It is also relevant to point out that since the early years of the twentieth century it had been known that cyanamides produce hypersensitivity to alcohol in workers in the cyanamide industry. In this industry, based on the Frank-Caro process, atmospheric nitrogen was transformed into calcium cyanamide, which is used as a fertilizer. The effect was first described by a German physician in 1914 and subsequently verified by other studies, but the causal mechanisms remained unknown; nor does anyone seem to have thought of cyanamide as a possible therapeutic agent in combating alcoholism.

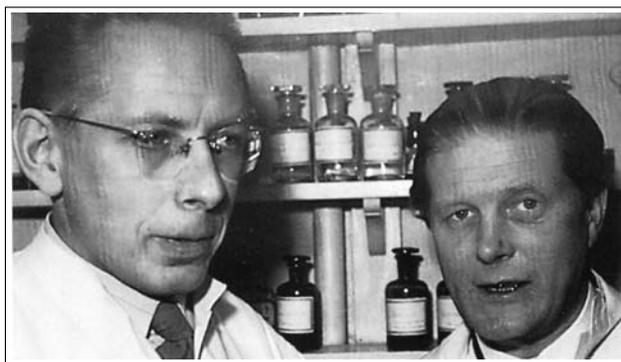
Apart from its use in the rubber industry, from the early 1940s disulfiram was also used in medicine as a scabicide. In 1942 two British physicians concluded that tetraethylthiuram monosulfide was a promising drug against scabies (9). The effect of the disulfide in destroying scabies, and possibly also intestinal worms, was investigated by Swedish pharmacologists, among others, who used disulfiram to cure domestic animals for scabies (10). The findings of the Swedish researchers were received with interest in Copenhagen, where the chemical company Medicinalco Inc. wanted to establish its own production of a disulfiram ointment capable of curing scabies. If the product could also be used as a vermicide, so much the better.

### The Discovery of Antabuse

Trained as a physician, Erik Jacobsen (1903-1985) specialized in biochemistry and worked from 1932-34 at Copenhagen University's biochemical institute, founded in

1928. In 1934 the 31-year old Jacobsen became head of the pharmaceutical company Medicinalco's biological-chemical laboratory, a center for biomedical research in the Copenhagen area. After having served industry in this position for nearly twenty years, he was appointed in 1962 professor of pharmacology at the Pharmaceutical College, an institution established in 1892 and recently merged with the University of Copenhagen.

During the German occupation of Denmark (1940-45), Jacobsen became interested in problems of cell oxidation, which he discussed with Jens Hald, a pharmacologist and experienced analytical chemist, who was associated with Medicinalco's laboratory and involved in research on the copper metabolism of intestinal worms. Jacobsen and Hald realized that the scabicide effect of disulfiram was due to its ability to absorb copper and form chelates with the metal. (It was known that in lower forms of life oxygen is transported by copper and not, as is the case in vertebrates, by iron.) They consequently reasoned that the drug would probably work also for intestinal worms, which at the time was a widespread nuisance not only for animals but also for children. Experiments with rabbits confirmed their suspicion that disulfiram was effective as a vermicide, leaving the substance to be tested also for intestinal worms in humans.



*Figure 1. Jacobsen (right) and Hald in Medicinalco's Laboratory, about 1950.*

What happened next was Jacobsen's decision to evaluate possible side-effects on himself, such as recounted in the article in *Time*. Hald had experienced a similar but weaker reaction, and the two researchers therefore suspected that the combined presence of disulfiram and alcohol was responsible. Jacobsen recalled (11):

It only took a few days to confirm that the disulfiram tablets really changed the effect of alcohol in a most unpleasant direction.

In the spring of 1945 Hald, Jacobsen, and their collaborators at Medicinalco vaguely realized that disulfiram might be used as a drug for alcohol treatment, but at the time they did not follow up the idea. They seem to have believed that alcoholism was not a major problem in Danish society and that an alcohol-deterrent drug was therefore of little commercial interest.

It was only two years later that the situation changed, mainly a result of the contact established in the fall of 1947 between Jacobsen and Oluf Martensen-Larsen, a physician who had experience with treatment of alcoholics. Collaborating with Martensen-Larsen, Hald and Jacobsen now initiated systematic studies in order to develop a disulfiram-based drug, to understand its physiological actions, and to establish its efficiency in clinical trials. Experiments confirmed that the disulfiram-ethanol reaction mainly took place in the liver, the most important organ capable of oxidizing ingested alcohol. As to the pharmacological actions of disulfiram, Hald and Jacobsen realized the crucial importance of acetaldehyde. According to Jacobsen's recollections nearly thirty years later (12):

One of our collaborators, a chemist, happened to enter the laboratory and pointed out the strong smell of acetaldehyde. We, being present in the room, had not noticed the smell because we had slowly adapted to it. This observation gave us the key to understand the process. Further experiments proved that when acetaldehyde was injected intravenously it resulted in the same symptoms as previously experienced. Enzymatic experiments proved that the oxidation of acetaldehyde, the first step in the oxidation chain of ethanol, was impeded by disulfiram in concentrations 1 : 10<sup>7</sup>.

One more accidental observation paved the way for antabuse. A sample of disulfiram had accidentally been polluted with small amounts of copper, and Jacobsen and his group noticed that the dark precipitate did not disappear by following the standard procedure of washing with ethanol. They succeeded in removing the precipitate by recrystallizing with carbon tetrachloride and in this way also securing a better drug. After the solvent had evaporated, disulfiram was left in a state with a much larger surface and therefore more easily absorbed in the organism. This form of disulfiram, named antabuse (or "antabus" in Danish), was granted a Danish patent in 1952, with patent protection retroactive from 1949 (13). The Danish version of the name was initially used also by English and American authors, but it was soon transformed into the Anglicized version.

## Disseminating a Drug

The discovery of antabuse, meaning the effect of disulfiram in preventing intake of alcohol, was announced to an international audience in an invited lecture Jacobsen gave to the annual meeting of the British Pharmacological Society on July 9, 1948. The following fall he and his group of researchers were busy with extending their studies of the many aspects of the disulfiram-ethanol reaction and publishing their results. Their productivity in 1948-49 was impressive.

The most important journal for the dissemination of knowledge concerning the actions of antabuse in the organism was the *Acta Pharmacologica et Toxicologica*, an international journal founded in 1945 and edited by Scandinavian scientists. The fact that it was published in Copenhagen and that Jacobsen was among the editors made it an ideal journal for publishing new research related to antabuse. For example, Vol. 4 of 1948 included two substantial papers by Hald and Jacobsen on the formation and action of acetaldehyde; and their collaborator Erik Rasmussen, a pharmacologist associated with Medicinalco, reported his investigations of the action of the antabuse-alcohol reaction on the blood circulation and respiration (14).



**Figure 2.** One of the early issues of *Acta Pharmacologica et Toxicologica*, the favorite journal of antabuse research.

Hald and Jacobsen measured the small amount of acetaldehyde in the blood of individuals treated with antabuse by means of a color reaction with *p*-hydroxydiphenyl. In order to be certain that the increase found was really due to acetaldehyde, and not to some other substances giving a similar reaction, they isolated and identified chemically acetaldehyde in the expired air. This they did by isolating and weighing the red-brown crystals of the derivative formed with an acid solution of 2,4-dinitrophenylhydrazine. In their study of 1948 Hald and Jacobsen demonstrated in this way an eightfold increase in aldehyde concentration in blood when 40 ml of alcohol was consumed after 1.5 g of antabuse was taken the previous day.

The medical world learned about antabuse by way of two companion papers by Jacobsen and Martensen-Larsen that appeared in *The Lancet* in December, 1948. According to Jacobsen's summary (15):

Alcohol given to persons previously treated with this otherwise innocuous substance produces dilatation of the facial vessels, increased pulmonary ventilation, raised pulse-rate, and general uneasiness. The symptoms appear to be the result of an increased formation of acetaldehyde from alcohol.

Martensen-Larsen reported on his clinical treatment of 83 patients in the period from December, 1947 to May, 1948. Since more than half of the patients benefited markedly from the treatment, he concluded that it was "promising." On the other hand, he fully realized that it could not stand alone. "The treatment with antabuse must often be only part of a general treatment," he emphasized (16).

This was also the conclusion of American and Canadian physicians who had followed the news from Copenhagen with great interest and conducted their own investigations. Erik Glud, a young Danish physician who was a resident in 1949 at the New Haven (CT) Hospital, wrote an article on the antabuse cure specifically addressed to American physicians. As he pointed out, because American drinking patterns were different from those in Scandinavia, the Danish treatment with antabuse needed to be modified before it was introduced in the United States (17).

At the annual meeting of the American Psychiatric Association, taking place in Montreal in May, 1949, three physicians from Albany (NY) Hospital described their antabuse treatment of 21 patients, all habitual drinkers, over a period of two to four months. As a result of the treatment, 14 of the patients discontinued the use of

alcohol entirely. "It is important to emphasize," they wrote, "that the chief value of Antabuse lies in the fact that it paves the way for psychotherapeutic procedures. ... Antabuse in conjunction with psychotherapy may prove superior to other methods of treatment of chronic alcoholism" (18).

### The Metabolism of Ethanol

Investigations of the action of antabuse and the fate of ethanol in the organism became a major research topic among the group of scientists in Copenhagen associated with Jacobsen and Hald. Whereas some of them focused on the clinical aspects, others studied the biochemical and pharmacological aspects. For example, Knud Raby, a young medical researcher, studied the disulfiram-ethanol reaction from a clinical point of view; and Erling Asmusen, a sports physiologist, did research on the pharmacological action of the acetaldehyde accumulated by the presence of antabuse (19).

Jacobsen occupied himself in particular with the metabolism of ethanol, a topic that attracted much attention at the time. In 1952 he published a comprehensive review of all aspects of the subject, and in January of that year he delivered an invited lecture on the topic at University College, London (18). The scientific study of ethanol's fate in the organism was of course not new. Important research had been done in the 1920s and 1930s, in particular by the Swedish chemist Erik Widmark, a pioneer of forensic medicine and chemistry (21). It had been established that the combustion of practically all ethanol takes place in the liver, and that the enzymatic oxidation to acetic acid occurs with acetaldehyde as an intermediate:



However, little was known of the reaction mechanisms or about substances that either promoted or inhibited the processes.

According to the new investigations, as undertaken in Copenhagen and elsewhere, ethanol is oxidized to acetaldehyde by means of the enzyme alcohol dehydrogenase (ADH); the acetaldehyde is subsequently transformed to acetic acid by the action of another enzyme, aldehyde dehydrogenase (ALDH). The principal action of antabuse is to block the action of ALDH, with the result of an accumulation of acetaldehyde (22):

"Antabuse" inhibits the flavin-containing aldehyde oxidases, and the aldehyde dehydrogenase, of the

organism. *In vitro* concentrations about  $1/10^7$  give a marked inhibition of the enzymatic actions, and the degree of inhibition is diminished with increasing concentrations of the substrates, suggesting a competition between “Antabuse” and aldehyde for the enzyme.

Among the first to establish the action of antabuse as an inhibitor for ALDH was Niels Ole Kjeldgaard, a 23-year old graduate student and later professor of molecular biology. In a series of experiments beginning in 1949 Kjeldgaard demonstrated that even in concentrations as small as  $0.1 \mu\text{g/ml}$  antabuse exerted a strong inhibition on the oxidation to acids by the liver aldehyde oxidases (23).

Among the results obtained by Jacobsen and his associates was the conclusion that a much larger dose of antabuse is required to block the transformation of ethanol to acetaldehyde than for the subsequent transformation to acetic acid. Even if the first process is impeded almost completely, it will not affect the transformation of aldehyde. Hald and his collaborator Valdemar Larsen, a pharmacologist, further found that other substances besides disulfiram act as inhibitors for the acetaldehyde-acetic acid process. It had been known for some time that cyanamide provoked disagreeable symptoms in combination with alcohol, and Hald and Larsen established that similar effects were produced by tetraethylthiuram monosulfide, tetramethyl disulfide, and a few other compounds similar to disulfiram (24).

The discovery of antabuse stimulated not only research in the metabolism of ethanol, but also other areas of a related chemical, pharmacological, and clinical nature. On the basis of a perusal of review papers and bibliographies, it is estimated that during the period 1948-53 about 140 research papers were written on antabuse and its effects; of these, about 40 were written

by Danish scientists and physicians. The research effort was of course international, involving scientists from the Scandinavian countries, the United States, Great Britain, Switzerland, Portugal, France, South Africa, Canada, and Austria.

### Uses of Disulfiram

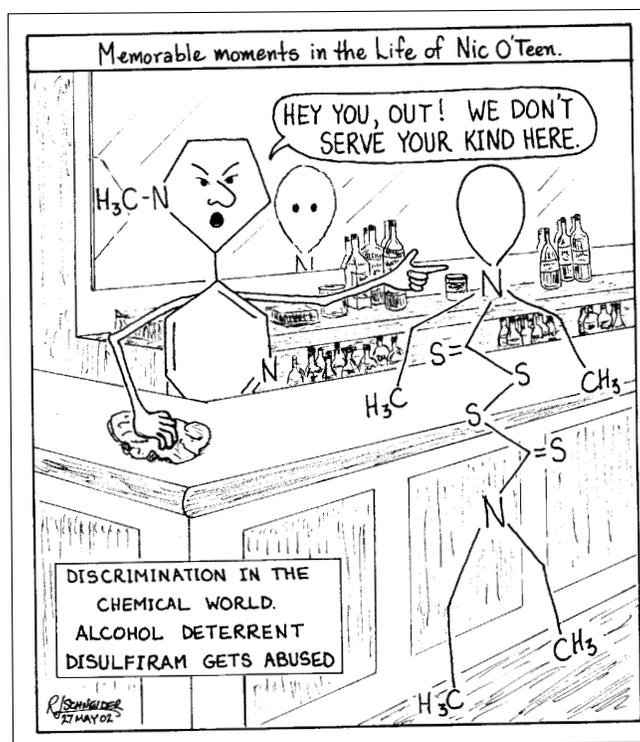
Treatment of alcoholism with antabuse was quickly introduced in the Scandinavian countries. In Denmark and Sweden, the drug was approved for medical prescriptions in early 1949 and generally looked upon with high expectations. In spite of the cautious attitude of many

physicians, the public tended to see antabuse – or abstynyl, as its equivalent was named in Sweden – as a kind of wonder drug. “Antabuse on its triumphant march throughout the world” read a headline in the Swedish newspaper *Dagen* of October 17, 1949.

Although the initial optimism soon waned, by the mid 1950s it had become the dominant procedure for treating alcohol misuse in the Danish health system. Antabuse was, and still is, to a large extent considered a “Danish drug” (25). There are a few other drugs with a similar effect (naltrexone and acomprosate), but these are only prescribed very rarely by Danish physicians. In the beginning

of the 21<sup>st</sup> century the total prescriptions per year in Denmark was 5 million daily doses, corresponding to an estimated number of 25,000 patients. The number of persons treated with naltrexone or acomprosate is less than 1,000.

In the United States antabuse was approved by the Federal Drug Administration in 1951, followed by approval of naltrexone in 1994 and acomprosate in 2004. According to a recent study, there are only about 250,000 disulfiram prescriptions (antabuse or some other brand)



**Figure 3.** Cartoon by Roger L. Schneider, from Amalgamator website (<http://alchemy.chem.uwm.edu/amalgamator/cartoons/>). Reproduced with permission of the artist.

written per year in the United States for treatment of alcoholism (1). Neither in the United States nor elsewhere is antabuse used on the same scale as in its country of origin. It is estimated that some 120,000 persons throughout the world take antabuse against their misuse of alcohol. About twenty per cent of them are from Denmark, a country of 5.3 million inhabitants.

The discovery of antabuse in 1948 stimulated research in therapeutic properties of disulfiram other than those related to preventing excessive drinking. As early as 1951, a research group under Henrik Dam found that antabuse had a beneficial effect on symptoms caused by a lack of vitamin E (26). A Nobel laureate of 1944 for his discovery of vitamin K, Dam served at the time as professor of biochemistry at Denmark's Technical University. While he continued his studies of vitamin K, in the early 1950s his main field of research was the nutritional and other effects of vitamin E (27). Dam's studies were further developed by the Danish odontologist Jens Pindborg, who, while working as a consultant for Medicinalco, showed that certain dental diseases caused by lack of vitamin E could be cured by disulfiram (28). Much research has recently been done on the therapeutic properties of the compound. It appears to have a significant potential in the treatment of human cancers and certain drug-resistant fungal infections (29).

Presently there is a strong focus on disulfiram's role in the treatment of cocaine addiction, both among patients who are alcohol-dependent and those who are not. According to Kathleen Carroll and her colleagues, the effect of disulfiram is not restricted to cocaine abusers who are also misusers of alcohol. On the contrary (30):

...disulfiram therapy might, paradoxically, be particularly appropriate for the treatment of cocaine problems among drug users who are not regular or problematic drinkers.

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