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Busy In The Meadow: [Dr. Vincent Dole]

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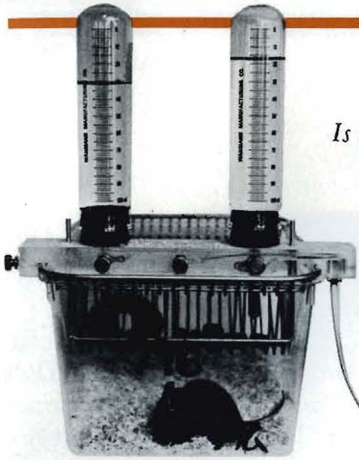
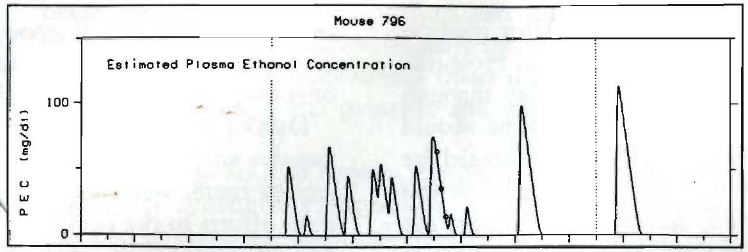


Is this mouse an alcoholic?



THE ROCKEFELLER UNIVERSITY

RESEARCH PROFILES

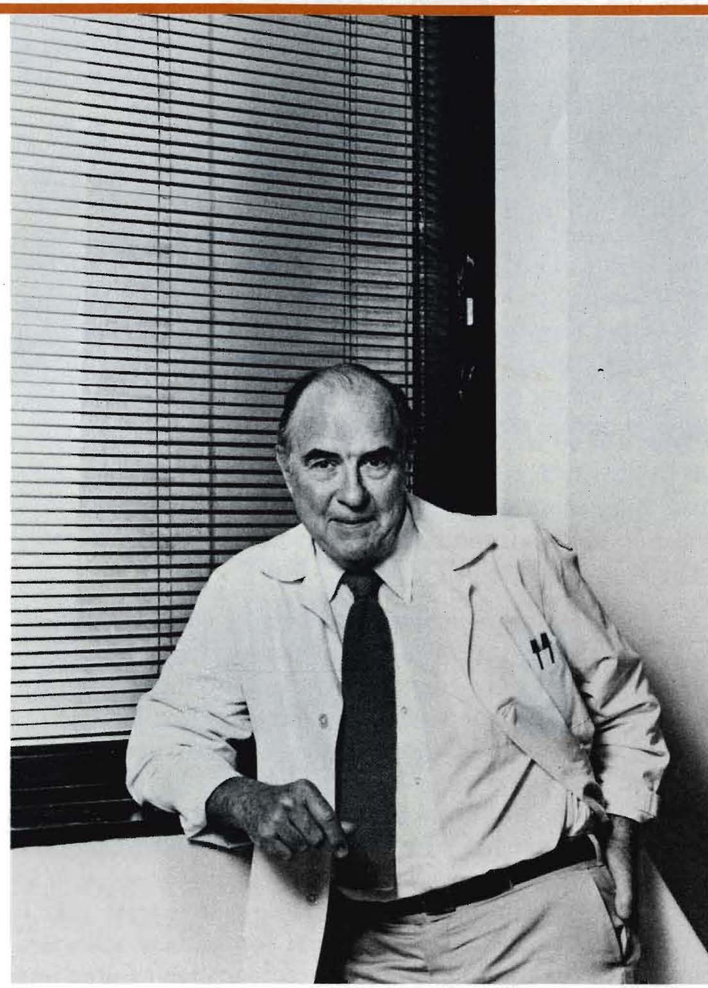
SUMMER 1983

Busy In The Meadow

Professor Vincent Dole confesses to a certain "tendency to meander." At various times he has explored kidney function, hypertension, obesity, sweat, the mechanisms of body energy, and the mathematics of electrophoresis. Nineteen years ago, after establishing such things as the culpability of sodium in high blood pressure and the unsuspected role of free fatty acids in body metabolism, he began inviting heroin addicts to The Rockefeller University Hospital. The result was methadone maintenance. Today at 70, still at work in the laboratory, he and his colleagues are trying to make mice alcoholic.

Although Dr. Dole jokes about meandering, comparing himself to "a kid in a big meadow who goes from flower to insect to tree," his course has not been quite so random or ingenuous. As his analogy suggests, he was drawn to biology through a fascination with the interdependencies of living systems. As a clinical scientist, he has channeled this fascination into studies that all broadly relate to metabolism—the complex, interacting processes of chemistry and physiology through which organisms utilize energy and maintain life.

Methadone maintenance as a treatment for heroin addiction is the achievement for which Vincent Dole's name is known to the public. But if methadone hadn't happened, he could still, as this profile does, look back on a distinguished career. He's been pretty busy in the meadow.



Vincent Dole

Vincent Dole and Marie Nyswander

Dr. Dole came to Rockefeller 42 years ago after medical training and a residency at Massachusetts General Hospital. He almost didn't make it. Having decided midway through medical studies at the University of Wisconsin that he should switch to the more research-oriented program at Harvard, he relinquished his place at the first before discovering there was no opening for him at the second. As a result, he spent the next year in his father's groves in California, learning to cure olives instead of people. "I probably would have stayed in the olive oil business," he says, "if my professor of pathology at Wisconsin hadn't meantime, without my knowing it, convinced the fellows at Harvard they'd made a mistake."

Mathematics runs a close second to biological research in Dr. Dole's affections. Before biology beckoned, he had planned to be a mathematician. In his early years at Rockefeller, he worked out a mathematical theory for determining the distribution of ionic constituents in electrophoresis, a method for separating and identifying ionized molecules in solution. His theory remains the standard model. Marie Nyswander, a laboratory colleague and his wife of 18 years, recounts finding him, one recent morning at six, feet up on the coffee table, eager to explain the topology of knots.

Thomas Gentry examines micro-samples of blood taken from mice for analysis of alcohol content.

BLOOD, SWEAT, AND FAT

Dr. Dole's first appointment at Rockefeller was in the laboratory of the late Donald Van Slyke, whose extensive contributions to clinical laboratory methods laid the foundations for many chemical and therapeutic procedures still in use.

"Van Slyke's contributions to the study of chemical processes in the body were so fundamental," says Dr. Dole, "that their roots are all but forgotten. He devised the tools and techniques he needed as he went along. His apparatus for the measurement of oxygen and carbon dioxide in solution in blood and other fluids was so simple and precise that it quickly became standard equipment for medical scientists. He introduced the concept of the reabsorption of urea into the bloodstream, a very good measure of kidney function. My first job in the lab was to work out some of the mathematics of reabsorption to make the clinical test more exact."

During World War II the Rockefeller Hospital was designated a naval research unit. Many of its scientists, Dr. Dole among them, were commissioned naval officers, and turned their efforts to the needs of the military. "Van Slyke saw that one important contribution our group might make would be to develop a quick, easy procedure that could be used in the field to measure blood density in shock victims in order to know how much fluid treatment they needed. We came up with a method that required only a drop of blood in a bottle of copper sulfate of known density. It was very ingenious. The New York Blood Center still uses it to determine whether someone has enough hemoglobin to be a donor."

After the war, with Van Slyke's retirement drawing near, Dr. Dole once again accepted a post at Massachusetts General. A year later, he relates, Thomas Rivers, then director of the Rockefeller Hospital, asked him to return as head of his own laboratory - to study whatever he chose with whomever he chose. "I told Rivers that I would like to work on hypertension. It was a disease for which some interesting treatments were being tried and one that clearly had to do with metabolism, which tied into my experience with Van Slyke. I asked Lew Dahl from Mass General to join me. Then George Cotzias, another Mass General colleague, simply announced he was coming, too."

Lewis Dahl left Rockefeller in 1952 to head the hospital at Brookhaven National Laboratories and went on to become a leading authority in hypertension. George Cotzias, who died in 1977, worked for many years at Brookhaven, Memorial Sloan-Kettering, and New York Hospital. In the Dole lab he began metabolic studies of amines, body chemicals important in nerve function. From work on dopamine he developed the drug L-dopa for the treatment of Parkinson's disease.

In the late 1940s, physicians were beginning to achieve some success in lowering blood pressure through diet manipulation. One theory favored a low-salt diet, another low-protein. In trials with patients, Dr. Dole and his associates traced

the problem to salt, and specifically to the sodium ion. The blood pressure of patients on the low-protein, low-salt diet went down, but it rose again when salt was added, while protein remained low. The low-protein diet did, however, lower the weight of those patients in the study who were obese. This raised questions in Dr. Dole's mind about the prevailing views on protein requirements, and so the laboratory began obesity studies. George Corner, in his history of Rockefeller, wrote: "One hardly knows whether to admire more the persistence of the investigators in carrying out the enormous number of chemical analyses required by this kind of research, or the willingness of obese women to live for months upon diets chosen for their specific content, with palatability a secondary consideration."

All of the patients lost weight on the protein-restricted diet, but they regained it after leaving the clinic. During his studies, Dr. Dole observed that markedly obese people don't necessarily overeat compared with people of normal weight; that, in fact, in order to maintain a normal weight after reduction, they have to live continuously on a calorically subnormal diet. The results of the subnormal diet are often depression and serious loss of energy. Why this happens–how metabolic and behavoral elements influence the development of obesity–remains a knotty problem in clinical research. Subsequent work at Rockefeller by Professor Jules Hirsch has helped explain a good deal about normal and abnormal fat-cell physiology. Dr. Dole's early observation that protein and nonprotein foods appear to interact to influence appetite is now being studied in a number of laboratories interested in the effects of nutrients on some of the recently discovered brain chemicals.

In the lab. Gathered around Dr. Thomas Gentry at the computer keyboard, left to right: Gwen Cohen, a summer helper, Assistant for Research Robert Jacobs, Dr. Dole, Dr. Sinisa Bogdanovic, a visiting pharmacologist from the University of Belgrade, Dr. Ann Ho, Dr. Michael Rappaport, and Assistant for Research Adrienne Chin.

The laboratory's hypertension studies also revealed that sweat gland secretions are altered by low-salt diets. Since little was known about sweat formation, Dr. Dole and his group proceeded, in the Van Slyke tradition, to devise methods for measuring concentrations of salts, urea, and other substances in sweat and for locating and counting the sweat glands.

Dr. Dole made an important contribution in the 1950s when he isolated free fatty acids in blood plasma and explained their role in carrying energy to tissues. Because their concentration in the blood is minute, free fatty acids had been considered by most researchers to serve little or no metabolic function. They were found, however, to have an exceptionally rapid turnover. Despite their low concentration, they were transporting a major fraction of the body's energy. Dr. Dole traced their origin to triglyceride molecules stored in fat cells and showed how they interact with insulin and carbohydrates, findings that have been important to understanding the events in arteriosclerosis.

"AN ABSOLUTE VACUUM OF DESPAIR"

In those years Dr. Dole became interested in a problem that, at first, appeared to be unrelated to his work. Each day, as he walked the streets of the city, he witnessed what he has described as "an epidemic growing all around me, drug addic-

tion." He soon learned that "most people, doctors included, considered addiction solely a psychological or sociological problem, a consequence of 'bad behavior,' or 'weak character.' Moreover, for decades, doctors who tried to treat addicts were harassed by government narcotics agents and threatened with the loss of their licenses."

Bad behavior was not a "useful" answer as far as Dr. Dole was concerned. "I had become sensitized to that kind of circular thinking when I worked with obese patients," he says. "It annoyed me to be told that fat people wouldn't be fat if they didn't eat so much. That's not a scientific explanation, it's a moral judgment. Then one day I was talking with Lewis Thomas, who at the time was chairman of the New York City Health Department's committee on narcotics. Apparently the department had decided that with so many addicts around, they ought to start thinking what to do. Lew was just going on sabbatical and suggested I take over the chairmanship, which I did. I spent a very educational year. By the end of it, I was persuaded that addiction was an attackable problem. The Health Research Council offered to allocate funds for research, so I went to Detlev Bronk, who was then president of the university, and explained what I wanted to do. I pointed out to him that we'd be inviting some rather unusual guests into the Rockefeller gardens, that we would probably be harassed by the Bureau of Narcotics, and that for those reasons it was a project no other institution wanted to touch. He replied simply: 'Then we will tackle the problem.' He never weakened his support. Looking into the field, the person I discovered with the most knowledge and experience of treating addicts was Marie Nyswander. I asked her to come to Rockefeller to help me set up my studies."

Dr. Nyswander's experience dated back to the 1940s when, fresh from medical school, she joined the service. "I wanted to fight Hitler," she says, "but instead I was sent to the federal prison hospital in Lexington, Kentucky, which was the only hospital in the country then, and for many years thereafter, where addicts were treated. The only treatment was detoxification. It wasn't very pleasant. After the war, I did a residency in psychiatry and went into private practice. I never wanted to see another addict. But I made the mistake of writing a paper on addiction for the *New England Journal of Medicine,* which made me an 'expert,' and I wound up seeing and treating thousands of addicts. I tried every approach—hypnosis, psychoanalysis, change of scene, you name it. My rich patients I sent to Paris. I worked for several years in a storefront clinic in East Harlem. I was the 'drug-addict lady.' It was a marvellous and touching experience. There wasn't much I could do except to arrange for detoxification, in some cases over and over again, but they were so grateful that someone cared."

The criminalization of addicts, of people Dr. Nyswander came to know as friends and whose struggles to survive she witnessed daily, frustrated and enraged her. Like Dr. Dole, she believed that medical treatment and research, not jail, offered the only hope.

In 1964, with the sympathetic and resourceful cooperation of Rockefeller's nursing staff, Dr. Dole and Dr. Nyswander

Adrienne Chin, left, and Ann Ho in the mouse room. Dr. Ho, a physiological psychologist, began work in the Dole lab as a technician while still in graduate school and became a member of the Rockefeller faculty in 1970. She conducted early studies of the sleep patterns of narcotics addicts and methadone patients. Currently she is analyzing the daily rhythm of eating and drinking of the experimental mice in the laboratory's alcohol studies.

The animals' cages, like the one shown in closeup on the front page, were especially designed for this research by Dr. Dole. They can be fitted with up to three bottles containing water and various solutions of alcohol or drugs. Each lick a mouse takes at a bottle generates an electrical signal to a computer. To reach the bottle, the mouse must rest a forepaw on a horizontal bar, which provides a ground for the electrical connection. This unique apparatus makes it possible to record minute-to-minute measurements of fluid consumption. It is simpler to maintain than conventionally wired cages, saving work time for the lab and disturbance to the mice.

Michael Rappaport filling a pump. When implanted under the skin of a mouse, the pump will deliver a continuous dosage of a drug. Dr. Rappaport is testing the effect of various drugs on the appetite for alcohol in the experimental animals.

began testing the effects of various narcotics, working with addicts who had volunteered to participate. In the course of their studies, Dr. Dole devised a urine test that is now routinely used to verify the presence and level of drugs in the body.

Opiate drugs such as heroin, morphine, and opium, and a variety of synthetic compounds, are pharmacologically grouped as narcotics. Although they quell drug craving interchangeably, their chemical structures differ and they are metabolized differently in the body. Heroin became the street drug of choice because its action is swift and intense. But its effect is short-lived: within a few hours drug hunger returns. Drug addicts develop tolerance, which means that as their systems adjust to a drug they require higher and higher doses. Therefore, most heroin users eventually must inject the drug intravenously.

Methadone is a synthetic narcotic, developed in Germany during the war as an analgesic to replace morphine. When Dr. Dole and Dr. Nyswander gave methadone to their patients, the effect was dramatically different from that of the other drugs they had tried. "Instead of sitting around irritable and jumpy waiting for the next fix or nodding in a dream world," Dr. Dole recalls, "the men began talking about baseball. One oral dose, taken in a glass of juice, stabilized them for 24 hours, and when they were on methadone, heroin had no effect. Their behavior became, for all practical purposes, normal."

A year after trials began, Dr. Dole and Dr. Nyswander reported in the *Journal of the American Medical Association* on their first group of 22 long-term addicts. They stated: "With this medication and a comprehensive program of rehabilitation, patients have shown marked improvement; they have returned to school, obtained jobs, and have become reconciled with their families. Medical and psychometric tests have disclosed no signs of toxicity except constipation."

"Methadone's stabilizing effect results from its slow elimination from the body," Dr. Dole explains. "Only about two percent is in the circulation at any time. The rest is held inactive in body tissues. As the active portion is excreted, the tissues release another small amount into the bloodstream. In that way the nervous system is not subjected to the sudden hammerblow rises in concentration typical of heroin."

The theoretical understanding of how methadone works and other studies that ascertained its medical safety took years of effort. Among those who contributed to this research from the beginning was a young physician from Cornell University Medical College, Mary Jeanne Kreek, who now conducts related pharmacological investigations in another Rockefeller laboratory.

The Methadone Maintenance Treatment Program was soon moved from its small experimental base at Rockefeller to Beth Israel Medical Center. There, and in other clinics, the number of addicts seeking treatment grew exponentially. In 1973 *Science,* the journal of The American Association for the Advancement of Science, reported that officials were "talking optimistically for the first time in the history of New York's heroin epidemic." James V. DeLong, former director of the Drug Abuse Council, a non-profit foundation, wrote a few years ago: "Before the Methadone Maintenance Treatment Program was developed, all treatment programs relied on some variation of detoxification, counseling or group therapy, and hope. But with all these methods, the results were terrible...So methadone maintenance did, in fact, puncture an absolute vacuum of despair."

Subsequent events have tempered expectations. The epidemic has not been eradicated. Dr. Dole attributes some of the early failures to ignorance of how methadone works, which resulted in patients receiving dosages inadequate to stabilize them. Other failures stemmed from premature or inappropriate attempts to detoxify patients, a procedure that, as experience has shown, succeeds with only a very small percentage of addicts. Many programs do not offer the social and backup medical services that Dr. Dole and Dr. Nyswander consider crucial at the beginning of treatment for people weakened and discouraged by years of illness and a marginal way of life. Further, it is impossible to estimate how many

have been discouraged or repelled by negative attitudes about methadone maintenance. In James DeLong's opinion: "The best programs seem to be those whose administrators take a matter-of-fact, nonpunitive attitude. The Dole-Nyswander approach is: 'You have a disease called heroin addiction. We are going to give you methadone, a medicine for it'... There is an immense gulf between this and a program operator who says: 'You, you weak-willed——, are an addict. If you insist on methadone we will let you have it, but your desire for it just shows how worthless you are.'"

At the introduction of methadone maintenance, Dr. Dole instituted exhaustive record keeping, later administered by an independent agency. The records show that, notwithstanding the problems, there are some 30,000 methadone-stabilized patients in New York. Many have been under treatment for 15 years or more. Dr. Nyswander tells of the distraught mother who, on learning her 17-year-old son, a heroin addict since age 13, was too young to be accepted into the program as then set up, responded: "Thanks a lot, Dr. Nyswander. If, four years from now, my son is still alive and he's not in prison, I'll send him to you." That conversation planted the seeds for the subsequent growth of the Adolescent Development Program, begun by Dr. Nyswander at Rockefeller and now in its own quarters under the direction of psychiatrist Robert Millman and pediatrician Elizabeth Khuri of New York Hospital. The boy who inspired the program has since finished graduate school.

Close to Dr. Dole's heart is the program for using methadone to detoxify prisoners in the city's detention centers. Designed as a humane alternative to "cold turkey," it was set up in 1971 with the help of volunteer methadone patients who worked for months without pay and often around the clock.

There is no cure for heroin addiction. Methadone maintenance is a treatment, as insulin is a treatment for diabetes. Two-thirds of the patients who discontinue methadone return to illegal drugs. The underlying knowledge that might lead to cures remains incomplete.

FROM THE BOTTLE TO THE BRAIN

There is no methadone for people addicted to alcohol. Nothing has yet been found in the existing pharmacopoeia, and Dr. Dole believes that a new substance may have to be synthesized. It will have to be tested on animals, but for the tests to have value the animals must be bona fide alcoholics.

"One of the first questions we've had to ask," Dr. Dole explains, "is whether our mice are taking alcohol as food or as a drug; because unlike other drugs alcohol has caloric value as well as pharmacological effect. It's a subtle question. To begin to find the answer, we had to establish a regular rhythm of eating and drinking under carefully controlled conditions. Our mice are kept in a constant-temperature room where the light is regulated night and day by computers and there's a minimum of disturbance. Then we ask: When we introduce a bottle of alcohol solution and they drink it, is the drinking fitting into the normal pattern of feeding and drinking? So far it seems to be, which implies that they're taking alcohol as food. To explore the implications of alcohol consumption further, we measure the concentration of alcohol being carried in the bloodstream and perfusing the brain. That information should help us determine whether the drinking is governed in any way by an *intention* by the mice to maintain a certain blood alcohol level in order to get a drug effect. To that end we've worked out microchemical methods. We bridge these occasional measurements—we don't want to do it too often because that in itself disturbs the normal behavioral pattern—with computer calculations about probable blood level. The computers are invaluable when you have licking data coming in continuously on 120 channels, generating millions of numbers. If ultimately we establish alcoholic behavior, *how* we established it will provide useful information. Did we do it by stressing the animals, by poisoning them with specific chemicals, by neurological lesions, or by some other reproducible manipulation? The answer may give us some clues about the way human alcoholism develops." □

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