Introduction of Niacin as the First Successful Treatment for Cholesterol Control, A Reminiscence

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Introduction

My years of training in internal medicine at the Mayo Clinic in Rochester, Minnesota began in 1950 and were interrupted by two years of active duty in the U.S. Naval Reserve, spent in San Diego from spring 1953 to spring 1955. Back in Rochester for a fourth year of training, I was serving as first assistant on the Peripheral Vascular Service at St. Mary's Hospital for the summer quarter of 1955 when a series of incredible coincidences culminated in an event that changed my life. No one had any way of knowing at the time, but it also changed millions of lives around the world.

The staff consultant on the service in August was Edgar V. Allen, a distinguished authority in the peripheral vascular field. Dr. Allen and his associates, Nelson Barker and Edgar Hines, had some years earlier written the bible of their specialty, *Peripheral Vascular Diseases.* Dr. Allen loved to teach. More often than not, when he met me and the four second assistants on the service, he would suggest that we sit and chat for a while before starting morning rounds. We never objected, for from these informal sessions came some of the most memorable teaching of our training years.

On this particular morning our chat was interrupted by a knock on the door of the conference room by Dr. Howard Rome, chief of the Section on Psychiatry at the Clinic, who was a duck-hunting buddy of Dr. Allen. He brought a surprising question: Would you be interested in hearing about a drug that reduces cholesterol levels? Skeptically (because there had been no successful drugs till then), we said that we would, of course, if there were such a drug. My mind quickly sorted through the short list of drugs that had been tried for this purpose. Thyroid had been tried but hadn't worked. Another agent which had also failed was a vegetable oil product, sitosterol, which one pharmaceutical company had marketed. I could think of no others.

The name of the drug surprised us, as Dr. Rome provided the few details he had. The preceding evening he had had dinner with Dr. Abram Hoffer, a psychiatrist from Regina, Saskatchewan, who had been in Rochester to give a series of lectures on schizophrenia. For years, he told Dr. Rome, he had administered large doses of niacin (then often called nicotinic acid) to his schizophrenic patients, feeling that it had helped them. Learning of this, his former anatomy professor at University of Saskatchewan, Dr. Rudolf Altschul, had suggested that he measure cholesterol levels in patients receiving niacin. Altschul, who had done studies of atherosclerosis in cholesterol-fed rabbits, predicted that niacin would reduce cholesterol levels. When his prediction proved correct, the two teamed with laboratory director Dr. James Stephen to try the drug in other volunteers. Their brief observations showed that niacin did, in fact, reduce cholesterol levels in a short period of time.

Early Niacin Use

Niacin was originally known as a member of the vitamin B complex which prevents the vitamin deficiency disease pellagra in humans and black tongue in dogs. It was in all the pharmacology textbooks and well known to doctors. Niacin was notable mainly because its administration, usually in 50 mg to 100 mg doses, was rapidly followed by flushing of the skin (redness of the skin of the face and neck, sometimes

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the whole upper body), accompanied by a very warm feeling, often with itching. For this reason, in vitamin preparations the closely related compound niacinamide (nicotinamide) was used because it had the vitamin activity without the flush. At that time niacin had practically no use in medicine other than its vitamin activity. Otolaryngologists sometimes recommended it for vertigo. Physicians sometimes hoped it might help patients who had experienced a thrombotic stroke. Mayo neurologists had studied this use, along with other agents alleged to dilate intracerebral blood vessels, but found that there was really no benefit. They acknowledged that the flush might make the family think that something was being done, although there was little that could be done for a stroke in those days. The fact that it was very safe seemed to justify its use, albeit as a placebo in those instances.

Niacin was made in 50 mg or 100 mg tablets. Our first thought was that the doses used by the Canadians, 1000 mg three or four times a day, would cause greater, intolerable flushing. Dr. Rome hastened to assure us that, according to Dr. Hoffer, flushing usually subsided in about three to four days and was no worse than with small doses. The Canadians had also briefly tried giving niacinamide. Although it caused no flush, it had failed to reduce cholesterol levels. Dr. Rome really had no further details, just these few important facts Dr. Hoffer had shared with him. It was evident that the Canadian originators had not performed a systematic trial to begin developing a useful method of treatment. Their specialties psychiatry, anatomy, laboratory science were not conducive to a clinical trial. On rounds that morning, I told Dr. Allen that although it sounded like a strange idea, we could easily test the claim that large doses of niacin could reduce cholesterol. In those days we did not have today's vascular surgery which can sometimes bypass occluded leg arteries.[4] Therefore we kept numerous patients in the hospital for weeks while we did everything medically possible to increase circulation, trying to heal ulcers on feet or legs. If our efforts failed and the leg became gangrenous, amputation was usually necessary, frequently above the knee. With so much at stake we often lavished weeks of hospital care, attempting to save a limb. One must remember that hospital charges at that time were reasonable.

Niacin/Cholesterol Trials

We customarily measured cholesterol and other blood lipids as part of our admission work-up, even though we had no good method for improving abnormal lipids beyond altering diet. Then, as now, diet was a weak and often ineffective way to reduce elevated cholesterol levels. I told Dr. Allen that I could recheck lipids on five or six patients with hypercholesteremia, tell them about the new treatment, and see whether we could verify the Canadian observations. Dr. Allen gave his blessing and promptly forgot about it. I have always been grateful for his approval.

I found five patients on the service with high cholesterol levels and a vascular status that would keep them hospitalized for several weeks. That afternoon, at the bedside of each patient I recited the fragmentary word-of-mouth report we had received and invited them to take part in a brief trial of a well-known drug, widely regarded as safe, to see whether it really did reduce cholesterol. I described the flush and assured them it would subside in a few days if our informant had been correct.

The patients agreed and began taking tablets (ten 100 mg tablets with each meal), after another baseline blood test. The flush lessened and disappeared in the first week, as predicted. So far so good. After one week I repeated the lipid studies and could not believe the striking reductions in cholesterol, triglycerides, and total lipids. In disbelief, I waited for the second week's results (as good or better) before showing the re-

sults to the others on the service. The initial hospital trial continued for four weeks, by which time it was apparent that a longer, carefully planned study was the next step.

The Mayo Clinic has a section just for care of Rochester residents. One of the young consultants in that section was my close friend, Dr. Richard Achor. He and Dr. Kenneth Berge (whom I hadn't met until then because he joined the staff during my two-year absence) had a list of patients with hypercholesteremia, which they gave me to recruit volunteers. By telephone I obtained 18 participants for at least 12 weeks of study, using niacin in 1000 mg doses with meals and measuring cholesterol weekly.

Laboratory scientist Dr. Bernard McKenzie brought a unique contribution to the study. His laboratory had been separating cholesterol fractions by electrophoresis, giving us a means of determining beta-lipoprotein cholesterol (now LDL cholesterol) and alpha1-lipoprotein cholesterol (now HDL cholesterol). Preliminary studies had shown that a high ratio of beta to alpha 1 cholesterol often led to premature heart attacks. We incorporated his testing into our study.

The results were just as impressive as in the preliminary hospital observations. There were marked cholesterol reductions in the first week in many, if not most, participants. Not only that, but the cholesterol fraction was the site of major reduction, accompanied by an increase in the fraction.

My Mayo colleagues encouraged me to report this promising new treatment before leaving Rochester in April 1956 to practice with a Madison, Wisconsin clinic. The paper I presented at a staff meeting was published in June in the *Proceedings of the Staff Meetings of the Mayo Clinic,*[1] the prestigious journal with world-wide circulation which has since then has shortened its name to *Mayo Staff Proceedings.*

At the time I realized that I was reporting the first successful cholesterol-lowering drug in history. My enthusiasm was tempered by the knowledge that it would have to be studied in many persons for years just to show that it remained effective, that it was safe in prolonged use, and that reducing cholesterol would, as we hoped, reduce atherosclerosis and prevent its disastrous complications.

A Fortuitous Chain of Events

Something I did not even consider at the time was the incredible series of coincidences that led to my first studying niacin's effect. Only later, in the 1970s, increasingly in the 1980s, and reaching a peak in the 1990s, did I fully realize that these circumstances came together like a string of beads to provide their eventual result bringing niacin to the attention of the medical world. If the scenario had developed in a slightly different way, the chain of events would have been broken, altering its conclusion.

To begin with, suppose Dr. Hoffer had not gone to Rochester just then to speak, after he and his colleagues had made some brief, unstructured observations which showed niacin's promise in cholesterol control. Suppose on his last evening in Rochester he had not sat with Howard Rome. Before becoming a psychiatrist, Rome had been a board-certified internist. He was especially interested in medications because Thorazine, then a new breakthrough drug, had begun to get people out of mental hospitals, introducing a new era of pharmacotherapy in psychiatry. What if Hoffer had dined with one of the analytical psychiatrists instead of Rome?

Suppose Howard Rome had not been on the St. Mary's Hospital service that month. And suppose that, even if he had, the Peripheral Vascular Service had been headed at that time by any other consultant instead of his duck-hunting buddy, Ed Allen. Would Rome have burst in and shared the news of niacin so readily? Suppose it had not been my quarter as first assistant on the Vascular Service. No one else in the room on that August day, all bright and capable Fellows of the Mayo Foundation, decided to confirm the Canadian observations.

But all these events did come together just as though planned, resulting in the Mayo study already described. What ensued in the following years made me more and more certain: It was meant to be!

The Mayo publication was important because it reported to its wide circulation the first systematic study, including the favorable results in the cholesterol fractions. Altschul, Hoffer, and Stephen had earlier published a letter to the editor of the *Archives of Biochemistry and Biophysics*[2] which might have been overlooked by clinical investigators and never implemented.

I first presented the updated Mayo report at the November 1956 meeting of the *American Society for the Study of Arteriosclerosis*, its first airing at a national meeting. (The ASSA later became the Council on Arteriosclerosis of the American Heart Association.) I first met Dr. Rudolf Altschul at their November 1957 meeting, saw him at any subsequent ASSA meetings he attended, and contributed a chapter to his book[3] on what was then known about niacin, which he was editing when he died in 1963. Of current interest, I recall his talk at the 1957 or 1958 meeting about his rabbit work, in which he showed that niacin strikingly reduced the foam cell content of atherosclerotic plaques. This is now especially significant in view of emphasis in recent years on rupture-prone plaques as a cause of sudden arterial occlusion, even when the narrowing is no more than 50% of the arterial diameter.

I had never met Abram Hoffer when, in 1990 we had a momentous telephone conversation which convinced me more than ever about my meant-to-be hypothesis. Something told me that summer to contact him. I learned that he had been in Victoria since 1976. Somehow he knew that I had been with Armour Pharmaceutical Company in Phoenix (1974-1978) after moving from Madison and before starting solo practice in Scottsdale. He had probably seen my address on one of the few papers I had published during those years.

The story of how niacin came to be tested in hypercholesteremia was stranger than I had expected. In 1952 Hoffer had experienced some bleeding from the gums, for which he had taken vitamin C without benefit. He had already been using niacin for schizophrenic patients and decided to take three grams daily to see how the flush felt. His gums improved. He reasoned that niacin had promoted rapid healing in gums which had been affected by chronic malocclusion and, with age, had not been healing as well as in earlier years.

Dr. Hoffer's use of niacin in schizophrenia began in 1952, at which time he was using three to six grams per day, as well as niacinamide. He called his work the first double-blind psychiatric study ever performed. In the mid-1950s he lived and practised in Regina. Dr. Altschul, who had been Hoffer's professor of anatomy in medical school at Saskatoon, had been doing oxidation experiments, exposing rabbits to ultra-violet light and to increased concentrations of oxygen in inspired air to see whether these measures would somehow alter cholesterol deposition in arteries.

On one occasion Professor Altschul sought to arrange a trial in humans for his idea that exposure to ultraviolet light might reduce cholesterol levels. He contacted his former student, Abram Hoffer, who was Director of Research for the province, and asked for his help in setting up such a study at Saskatchewan Hospital, a 1600-bed mental hospital in Wayburn. They planned a joint visit to the hospital for this purpose. Dr. Altschul took a train to Regina, and together they drove to Wayburn, 71 miles away.

During the drive they talked about their individual interests. Altschul expressed his opinion that atherosclerotic plaques developed because of injury to the intima. He went on to speculate that the intima was not healing fast enough. Hoffer suggested a trial of niacin, based on his

personal experience with bleeding gums.

In our telephone conversation, Hoffer told me that when he made his suggestion, Dr. Altschul didn t know what niacin was! Having received large quantities of niacin and niacinamide for his work, Hoffer gave a pound of niacin powder (about 450 grams) to his former anatomy professor, who then fed it to rabbits whose blood cholesterol had been elevated to very high levels by dietary maneuvers well known to animal researchers. How he knew how much niacin to use is among the bits of information still lacking, but apparently niacin reduced the blood cholesterol levels within days. Hoffer reported that Altschul then phoned him, excitedly shouting, "It works! It works!"

Until that September, 1990, conversation I had never known who Jim Stephen was. Hoffer explained that he was the chief pathologist and laboratory director at the hospital in Regina where Hoffer practised.

With his permission, in 1954 Hoffer did a two-day study, giving niacin to about 60 patients who demonstrated a reduction in their cholesterol levels. Altschul, Hoffer, and Stephen then wrote their letter to the editor of *Archives of Biochemistry and Biophysics.*[2]

Hoffer's story ended where mine had begun. In August 1955 he went to Rochester, invited by the Mayo Foundation to give a series of three lectures on schizophrenia. He confirmed that on his last night in town the Section on Psychiatry had taken him to dinner, where he happened to sit with Howard Rome. Tired of talking about schizophrenia, he mentioned his niacin experience. Hoffer's incredible series of coincidences merged with mine. Bringing niacin's striking cholesterol-reducing properties to the attention of the medical world was meant to be.

In our phone conversation, I picked up the story and told Hoffer of the chain of events which had brought his information to me and resulted in my decision to do further studies. He had never before heard the details. He had many complimentary comments about my research in the following years, correctly recognizing that it had provided the impetus that resulted in niacin's becoming a major cholesterol-control agent. We closed our telephone conversation with the mutual wish that we might some day get together to discuss our shared interests face-to-face.

In the fall of 1997, a medical association in Victoria to which Dr. Hoffer belongs invited me to speak to them and the public about my work with niacin and my forthcoming book, *Cholesterol Control Without Diet! The Niacin Solution*, scheduled for publication late in 1998.[4] This was the pilgrimage I had always envisioned, to meet Dr. Hoffer. We used it for a dual purpose, which included beginning the promotion for the book. I finally met Abram Hoffer in person for the first time in the driveway of the Empress Hotel in Victoria, on November 11, 1998, more than 43 years after my first use of niacin for hypercholesteremia. It was his 80th birthday. He and his wife, Rose, took my wife, Lynn, and me to their favorite restaurant for a wonderful dinner and evening, along with Dr. Peter Nunn, chair of the group whose invitation had prompted the trip. We reviewed the circumstances that had brought us together and all that niacin had come to mean to doctors and their patients around the world. We hoped that my book would teach patients the importance of niacin's distinctive advantages, not shared by any other cholesterol-control drugs, and also show doctors how to become proficient at using niacin.

The people of Victoria were wonderful. Their interest in the book was rewarding and encouraging. After my talk, I presented Abram Hoffer with a plaque that read:

ABRAM HOFFER, M.D., Ph.D., FRCP(C)

Your use of niacin for schizophrenia led to its use to control cholesterol. By taking the idea to the Mayo Clinic, you allowed others to develop this treatment and introduce it to the medical world. Niacin has prevented many heart attacks, strokes, car-

diac operations, and deaths. You deserve the gratitude of many, whose lives have been saved or improved by your message. It Was Meant To Be!

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I have always been happy to share with the Canadian originators whatever credit there may be for pioneering the use of niacin for cholesterol control and for its eventual reduction of heart attacks (24%), strokes (26%), cardiovascular surgery (46%), and deaths (11%, adding a mean of 1.63 years of life to men 30 to 65 with one or more preceding heart attacks).[5] Without their vision and Hoffer's taking their observations to the Mayo Clinic, I would not have been able to perform the first systematic study and follow it with further research in Madison, leading to the Coronary Drug Project's demonstration of niacin's preventive effects in cardiovascular disease.[6] Dr. Hoffer has correctly said that while pioneers in many fields argue about precedence, we are friends who readily acknowledge each other's roles in starting niacin research. Clearly, it was meant to be.

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