The Discovery of Heparin

By JAY McLEAN, M.D.

The DISCOVERY of heparin came as a result of my determination to accomplish something by my own ability. Just when this motivation arose in me and what factors nurtured this determination, which was not necessarily fully developed before I went to Johns Hopkins, are difficult to date. I believe the mile posts were the death of my father, John T. McLean, M.D., when I was 4 years old, the remarriage of my mother when I was 9, the earthquake fire in San Francisco when I was 15, the letter of my stepfather when I was 22 discontinuing any further support of my studies in 1922, and a talk with my cousin, Herbert McLean Evans (my father’s sister’s son), on academic behavior as a student at Johns Hopkins.

I was reared without a father, and a child knows when there is no breadwinner to rely upon. My stepfather was unsympathetic to my plans for a medical education at Johns Hopkins. The earthquake and fire in San Francisco in 1906 stripped us of all accumulated assets; our house burned, my stepfather’s place of employment burned, and the outlook was stark.

Despite these handicaps, I made the decision to become a physician during my last year at Lowell High School in San Francisco (1908-1909). At this time I read Flexner’s Medical Education in the United States. I have remembered he described the ‘chem lab’ of one school as ‘consisting of a cigar box of broken test tubes.’ I entered the University of California at Berkeley (1909), and while there firmly hitched my future to Johns Hopkins Medical School and a career in academic surgery.

At that time (1911) one could enter the University of California Medical School with two years of college preparation, but Johns Hopkins required at least three. I was forced at the end of my sophomore year, May 1911, to make the choice. My stepfather argued that the University of California Medical School had sufficed for my father (M.D. 1867) and for his 15 year old brother, Robert Armistead McLean (M.D. 1876), Professor of Surgery and Dean, Emeritus, in 1911. After his death in 1918, he was honored in the medical literature as ‘California’s First Master Surgeon.’

My argument was that Johns Hopkins offered me more preparation in the field of academic surgery, that is, research and teaching, for a lifetime career. Also I felt deeply the responsibility of being a physician. I doubted if I possessed the qualifications to become one; and I deliberately chose the fiercest student competition, as Johns Hopkins’ matriculants were meticulously chosen.

My stepfather had paid for my board and room, $27.50, during my freshman and sophomore years at college; the rest I earned. He offered to continue this for four years of medical school at the University of California in San Francisco. If I had decided to go to Johns Hopkins, his aid would be stopped at the end of my sophomore year, May 1911.

Summer work would not yield enough in savings to finance my third college year, so I was forced to leave college for fifteen months. Some of my Sigma Chi Fraternity brothers were going to the Mojave Desert gold mine, The Yellow Aster, at Randsburg, for practical experience in mining engineering. I followed them—got a job as ‘mucker’ (twenty-five cents an hour)—rose to chuck-tender, apprentice miner, and then to a millhand, where we processed the ore into beautiful gold bricks. I stayed there until August 1912, fifteen months in all, with enough money saved to re-enter college then for the third year of preparation for Johns Hopkins. My spare time was devoted to various part-time jobs. Robert Sproul, now President of the University of California, and I both worked in the Recorder’s office. I did blood counts and urinalyses in the College Infirmary, worked in the Museum of Invertebrate Zoology, and book-stores. I also worked scrubbing the decks of ferry boats plying in San Francisco Bay.
lumberyards, and as Railway Mail Clerk from Oakland to Denver. All of this was not new to me as I worked at various odd jobs since the age of twelve.

In the fall of 1913 I commenced my final year at the University of California which was concurrently my first year as a medical student, and was graduated May 1914 with a B.S. degree—but "broke" again. My ill uncle, Robert Armistead McLean, sat with the faculty on the stage of the Hearst Greek Theater. One of my subjects in the first year of medicine was physiology under Professor Maxwell. Howell's textbook was used. I was fascinated with the subject and its research possibilities. I wanted to do some research there; but all my spare time was devoted to my job as a technician in the clinical pathology laboratory at the College Infirmary.

I applied for admission to Johns Hopkins but later learned that my dean at the University of California had written the dean at Johns Hopkins that "I was not the kind of man Hopkins sought." In addition, I had no money for the transcontinental journey, let alone the expenses for an academic year at Johns Hopkins.

So I returned to remunerative labor, this time drilling oil wells. Manual labor paid so much more than "white collar jobs" and living costs were lower—hence producing greater savings for my purpose.

Again, after fifteen months of work, I had funds for one year at medical school. Even though I had been notified I was not acceptable as a student at Johns Hopkins, I bought a ticket from San Francisco to Baltimore and went there after paying off a senior class loan to the University of California.

I arrived in Baltimore one Sunday morning at Port Royall Station and trudged with my suitcase to the Washington Monument, the first to be erected to him in the United States, and to the Stafford Hotel nearby. My object in going to Baltimore, knowing that I had been rejected for admission to the second year class was twofold. I reasoned that I could work a year there as well as in California; secondly, after my 1914 graduation from the University of California, Johns Hopkins had added organic chemistry lab to lectures as a requirement for admission. Working in the oil fields, I could not acquire this subject. I calculated I could work in Baltimore and make this up at Johns Hopkins University at Homewood.

Monday, the next day, I went over to Johns Hopkins Medical School and Hospital and introduced myself to Mr. Coy, the Registrar, and to Dr. W. Williams, the Dean. Then I arranged to share a room on Biddle Street with Irwin Schumacher, now on the faculty of the University of California in San Francisco. Arnold Rich, now Professor of Pathology at Johns Hopkins, and James Cash, now Professor of Pathology, University of Virginia, were roommates next door. Mr. Coy was surprised to see me and asked if I had not received the letter denying me admission. I told him I had, but figured on working a year; and I started to look for a job. The next day word was sent to me to see the Dean. I was informed there was an unexpected vacancy and I had been admitted to the school in the second year of medicine.

I promptly paid the fees for a year as a medical student, taking no medical school courses. I immediately called on Dr. Howell and told him of my desire to prepare for an academic career in surgery and that I wished to devote one whole year to physiological research now. I felt that I could never do it after graduation for that would interfere with the house officer progress on a surgical staff. I told him then that I wanted a problem I could reasonably hope to finish and publish in one academic year entirely by myself. I wanted to determine if I could solve a problem by myself. I told him my savings would just last one year, and after that I would have to work a year before returning to school.

He gave me the problem of determining the value of the thromboplastic substance of the body. He thought this to be kephalin (cephalin), obtained from brain but, of course, knew the thromboplastic material from brain to be a mixture—a crude extract, though a powerful thromboplastic agent. He made this by macerating brain tissue, spreading it on glass panes, drying it over a gas flame in an oven, extract-
ing it in ether, decanting, concentrating the ether extract, and finally by precipitation with alcohol. This precipitate was his thromboplastic substance. He used it in blood-clotting experiments. It was kept in a glass vessel with ground glass cover (vaselined), as it was observed that access of air decreased its ability to accelerate clotting. In three months it was decayed.

My problem was to determine what portion of this crude extract was the active accelerator of the clotting process and to that end, to prepare cephalin as pure as possible and determine if it had thromboplastic action. I was also to test the other components of the crude ether-alcohol extract. I was assigned a sink and attached "table-drainboard" with a shelf over the sink in a large student physiology laboratory (not used as such then) across the hall from Dr. Howell's office and private laboratory.

Others working in the department at the time (1915) were Charles Snyder, Donald Hooker, Cecil and Mrs. Drinker, and Stanley Cobb. I was held distantly by them, except by Dr. Snyder. They, with Dr. Howell, worked together, but I was not invited to join them. I was not a colleague. This may also have been in part because my drying tissues produced an all-pervading insufferable odor which penetrated throughout the laboratories on the floor and to Dr. Abel's laboratory on the floor above!

At the same time I started the organic chemistry laboratory course, to wipe out an entrance deficiency, and voluntarily took an advanced course in German, the better to read the German chemistry literature on lipoids. Hugh MacLean's book, however, was in English.

It was this determination to become a physiology-based surgeon rather than an anatomy-based surgeon that led to the discovery of heparin. In those days, 1912-1913, anatomy was considered the main foundation for surgery, as it had been for Robert A. McLean and my father.

My key decisions were thus as follows:

1. Study medicine.
2. Academic career.
4. Physiology.
5. Investigate the brain and other organs for thromboplastic agents.
6. Study for deterioration of cephalin.
7. Save these longer in event heparin action came up (dog experiment).

In 1915 my cousin, Herbert McLean Evans, M.D., Sc.D., moved from Johns Hopkins to the University of California as Professor of Anatomy. I met him for the first time the day before I left for Baltimore. He gave me the following advice: "Ask no questions but look up for yourself what you want to know." He gave me many letters of instruction to his friends, members of the faculty at Johns Hopkins. Except for one to Dr. Howell, I did not present them as I wanted to progress by my own efforts.

I worked nights, Saturdays, and Sundays and the first steps of my problem were completed in December 1915. I still had enough money for board and lodging until June 1916 so I could continue to work in research without receiving any stipend from the medical school. I suggested to Dr. Howell that it might be profitable to extract the lipoids (phosphatides) from many different organs. I reasoned that as cephalin could not be crystallized, one could not be sure of its purity and hence, its function as the thromboplastic substance of the body. However, if the thromboplastic activity of brain extract were due to some other substance, adherent to or absorbed by cephalin, this might not be so in organs which did not contain such a large amount of cephalin as the brain does.

In my reading of the German chemical literature on phosphatides, I found articles by Erlandsen and Baskoff in which they described extracts of heart and liver secured by a process similar to that for obtaining cephalin from brain. Therefore, these products might be heart and liver cephalin, but were named cuorin (from the heart) and hepaposphatide (from the liver); hence the name heparin. I suggested this research problem as a logical supplement to the problem Dr. Howell had given me. He had not known about cuorin or hepaposphatide.
I first prepared cuorin. The final extract was brown, not white or yellow like cephalin. It was waxy. It was a powder. It did not smell "fishy" as does cephalin and although it accelerated the clotting of blood somewhat, it was not as powerful as brain cephalin.

I then prepared Baskoff's heparphosphatide with a similar result. As in the brain, the more "purifications" done (ether extract into hot alcohol), the weaker the thromboplastic activity became. The same process of extraction was used for brain, heart, and liver, yet in the brain, the end product was almost all cephalin, but in the heart and especially in the liver it was something else which was mixed with cephalin. As cephalin is powerful, a small amount of it gives ample evidence of its thromboplastic power. Many batches were made of both cuorin and heparphosphatide. By this time, what little cephalin remained from my former studies with brain tissue was deteriorated by the process of extraction plus air and time. I was about to go on to the extraction of cephalin from the uterus and skin. I had saved batches of cuorin and heparphosphatide and from time to time tested these in serum plasma to determine whether or not the cephalin from the heart and liver deteriorated and lost its thromboplastic power as did that from the brain. If I had not saved them, I would probably not have found heparin.

This was a fortuitous decision. All I was trying to prove was that an ether-soluble, alcohol-insoluble extract of cephalin would accelerate coagulation of blood, and it did.

I became interested in the deterioration of cephalin (an unsaturated fatty acid), which I assumed became saturated on exposure to air (and ether-alcohol purification). It seemed sound to determine the iodine number of fresh cephalin in various stages of its decay down to no activity—about 3 months—by exposure to air. This Arbeit was completed and published the following year (1916-1917) at the University of Pennsylvania.

The various batches were tested down to the point of no thromboplastic activity, but two of those first prepared appeared not only to have lost their thromboplastic action, but actually to retard slightly the coagulation of the serum-plasma mixture. I had in mind, of course, no thought of an anticoagulant, but the experimental fact was before me; and I retested again and again until I was satisfied that an extract of liver (more than heart) possessed a strong anticoagulant action after its contained cephalin had lost its thromboplastic action.

At first I said nothing to Dr. Howell about this. It was not part of my planned problem, and it took time to satisfy myself. I had been working alone, in no wise assisting Dr. Howell. He was then engaged much of each day in a dark room watching precipitates of fibrin form through a microscope.

After more tests and the preparation of other batches of heparphosphatide, I went one morning to the door of Dr. Howell's office, and standing there (he was seated at his desk), I said, "Dr. Howell, I have discovered antithrombin." He smiled and said, "Antithrombin is a protein, and you are working with phosphatides. Are you sure that salt is not contaminating your substance?"

I told him I was not sure of that, but it was a powerful anticoagulant. He was most skeptical. So I had the Diener, John Schweinhaut, bleed a cat. Into a small beaker full of its blood, I stirred all of a proven batch of heparphosphatides, and I placed this on Dr. Howell's laboratory table and asked him to tell me when it clotted. It never did clot.

He still did not believe that I had discovered a natural anticoagulant, but it was at this point that he became associated in my research problem, namely the study of the effects of my anticoagulating substance (heparphosphatide), which gave greater yield and higher anticoagulating potential than cuorin in vivo in dogs. When I demonstrated new batches to him in vitro, and be became satisfied that it did actually inhibit the coagulation of the serum-plasma test mixture as well as whole blood in vitro, we planned the first in vivo experiment with a dog and administered the heparin intravenously.

(This was as far as Dr. McLean progressed in his history of the discovery of heparin before he developed his fatal illness and died November 14, 1937.—Ed.)
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Circulation. 1959;19:75-78
doi: 10.1161/01.CIR.19.1.75
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/19/1/75.citation

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