

LOYAL DAVIS, SURGERY OF THE LIVER AND TRANSPLANTATION OF THE KIDNEY

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IN THE DEVELOPMENTS in organ transplantation and hepatic surgical treatment of the last quarter century, Loyal Davis played a peripheral, but by no means insignificant or passive, role. During the first part of this period, Doctor Davis was chairman of the Department of Surgery at Northwestern University, and throughout almost all of it, he was Editor-in-Chief of SURGERY, GYNECOLOGY AND OBSTETRICS. The fact that he functioned in these two powerful administrative positions in an intelligent and creative way was part of the explanation for his long tenure in both offices.

In these reminiscences about Doctor Davis, I will focus upon the five year period from 1958 to 1963, even though our acquaintance was more than casual for a decade before this time and for all the years after. Between 1947 and 1952, I had been a student in the M.D. and Ph.D. programs at Northwestern. I met Doctor Davis within the first week of my arrival in Chicago. He was a terrifying figure to many of the students. He developed an interest in me because he realized that I was working toward a Ph.D. in neuroanatomy as well as trying to go to medical school. In my senior year, I spent my surgical clerkship at Passavant Hospital on Doctor Davis' service and learned more about surgery during those three months than in any other similar period of my life.

I graduated from medical school in 1952, spent the next six years in Baltimore, Maryland, and Miami, Florida, and returned to Northwestern in July 1958 for a one year appointment as chief resident in thoracic surgery. After this, I joined the faculty as the second full-time appointee in the Department of Surgery of which Doctor Davis was chairman. Doctor F. John Lewis, the cardiac surgeon, had been the first such appointee in a department that previously had depended upon the contributions of volunteer faculty to train students and house officers.

The recruitment of surgeons for whom the medical school provided a base salary was a policy change which created understandable political problems for Doctor Davis. These concerned the extent to which the so-called full-time faculty members, who were viewed by many as tainted from university subsidization, should be allowed to compete for private patients who needed conventional surgical care.

In defusing the situation, Doctor Davis made clear to me his desire that I develop a major and visible program in laboratory investigation. The result was an unparalleled opportunity to begin work in several seemingly esoteric areas that have occupied my attention for almost all of the 25 years since then. Even though he was a neurosurgeon, Doctor Davis watched carefully the work that was going on in the laboratory. For more than two decades subsequently, he kept close track of the developments which he realized had had their genesis under his original sponsorship.

HEPATOTROPIC FACTORS AND SURGERY OF THE LIVER

Compared with today, grantsmanship in 1958 was a primitive and ingenuous art form. During that year, while still a thoracic surgical resident under Doctor F. John Lewis, I sent a four page grant application to the National Institutes of Health requesting funds of about \$30,000 a year for five years. The objectives were to investigate if insulin had different effects if it was given by the portal versus the systemic venous system, to study the effect of endogenous insulin upon the liver and its metabolism and to look at the possibility of ameliorating disorders of insulin and carbohydrate metabolism by portal diversion procedures. The money was awarded.

In retrospect, it is surprising that support was provided. The rationale for the proposal was counter-current to the prevailing opinion which held that portal venous blood contained no specific substances that distinguished it in an important way from other kinds of venous blood. Complications, such as encephalopathy, were well known to occur after portacaval shunt in dogs or in humans, but these were thought to be the consequences of loss of volume of hepatic blood flow after portal diversion rather than the loss of special portal constituents. The underlying assumption in the grant request was

radically different. It suggested that splanchnic venous blood returning from the nonhepatic splanchnic viscera was capable in a special way of influencing hepatic structure and function. In later years, this concept became known as the hepatotrophic hypothesis.

No support could be found in the Northwestern laboratories for the hepatotrophic hypothesis for the simple reason that appropriate experimental models had not yet been developed with which to test the theory. Yet, Doctor Davis always remembered the original question. As the pieces fit into place showing, first, that portal venous blood had specific liver supporting qualities and, second, that these qualities were due to hormones (especially insulin) coming from the nonhepatic splanchnic organs, he published the evidence in *SURGERY, GYNECOLOGY AND OBSTETRICS*. He lived long enough to see hepatotrophic physiology become a defined field of research with numerous implications in clinical medicine (1).

One afternoon in 1959, Doctor Davis asked me to his office and asked a number of questions about the conditioning which my animals had gone through before their use in experiments. He was also concerned about the postoperative dietary management. The chairman of biochemistry at Northwestern, Doctor Smith Freeman, had been studying various aspects of the metabolism of Eck's fistula. Doctor Davis told me that he had been discussing my work with Doctor Freeman and that, as a consequence, he was raising the issues of animal preparation and maintenance in an effort to be helpful. After that, he made a number of visits to the kennels on the 14th floor which resulted in a sharp increase in the attention paid by the deiners to details of care.

TRANSPLANTATION OF THE LIVER

In order to pursue some of the inquiries about hepatic physiology which were on my mind in 1958, it was necessary to have a reproducible experimental preparation of total hepatectomy. I developed a method for use in dogs that differed from any previously reported technique in that the retrohepatic vena cava was left intact. The portal system was connected by vascular anastomosis to the vena cava. The procedure has become widely used in laboratory experimentation. In addition, it was realized as a direct consequence of these efforts that it might be possible to replace the extirpated liver with a hepatic homograft. Many of the technical details of total hepatectomy and transplantation were similar, including the use of a venovenous bypass from the lower to the upper half of the body of the animal which allowed temporary decompression of the surgically connected portal and systemic venous beds.

In the summer of 1958, the first efforts at orthotopic hepatic transplantation (hepatic replacement) were made in dogs. The project would have discouraged a more experienced or intelligent investigator, since the first 27 procedures resulted in operative deaths of the recipients. However, the two principles essential for success were finally worked out. One was protection of the venous beds of the intestine, kidneys and hindquarters during the period of venous occlusion as the new liver was inserted; this was accomplished by more efficient venovenous bypasses. The other principle, effective graft preservation, was met by core-cooling the liver with cold lactated Ringer's solution. This simple preservation technique became standard for laboratory transplantation research with other organs and in clinical renal transplantation.

Once the technical principles essential for success had been defined (2), the operation of hepatic replacement could be studied in detail. Methods could be tested for the prevention of the rejection process which was the next great barrier to be surmounted. In the Chicago series of untreated canine liver recipients, the maximum survival period before death from rejection was 20 and a half days.

Efforts to prevent rejection with total body irradiation of the recipient (or of the graft) were completely unsuccessful. It was not until 1963, after I had moved to the University of Colorado, that prolonged survival periods were achieved using drug therapy with azathioprine. In 1964 and 1965, animals which were treated with this drug or later with antilymphocyte globulin began postoperative lives that lasted more than a decade and were terminated by old age.

At Doctor Davis' suggestion, the results of the experimental studies on transplantation of the liver from the Northwestern laboratories were published in *SURGERY, GYNECOLOGY AND OBSTETRICS* (2). It could not have been too surprising to him in the autumn of 1963 to receive a report of the first clinical trials with this procedure; he accepted the article for publication by return mail (3). Replacement of the liver has become an increasingly successful way of treating end stage hepatic disease (4, 5).

TRANSPLANTATION OF THE KIDNEY

During the Chicago period of 1958 until 1961, liver transplantation received major attention from me because of its unique and challenging technical requirements. At the same time, we were conducting experiments with renal, splenic and composite organ grafts. These efforts were known to Doctor William R. Waddell, who was recruited as department chairman from Harvard to the University of Colorado in July 1961. Doctor Waddell asked me to join him and to become the Chief of Surgery at the Denver Veterans Administration Hospital which I did in December 1961. About a month earlier, Doctor Waddell persuaded one of the internists at Colorado who had a patient with advanced renal failure and a possible identical twin donor to hold this potential transplant recipient until my arrival. Within a month, the first of the Colorado renal transplants was carried out for the patient. This was not a major achievement since there was not an immunologic barrier, but within a little more than a year, ten more patients had been treated, all with nontwin donors. When I left Colorado 19 years later, six of the 11 recipients were still alive.

The excitement of those days is hard to imagine for those who were not there. Before then, azathioprine had been used clinically by Murray and associates (6) in a few instances, but as a single agent, the drug did not prevent rejection consistently or even in a significant number of patients. The literature about renal homotransplantation was uniformly pessimistic. The patients treated in Colorado were the first to have the double drug therapy of azathioprine and prednisone systematically which became the worldwide standard for immunosuppression. With the use of these synergistic agents, an avalanche of new information was forthcoming about the reversibility of rejection, the "adaptation" that occurs after successful transplantation and a multitude of other important events (7).

In the late spring of 1963, a manuscript about this early experience was submitted to the *Journal of the American Medical Association*. As a courtesy, I sent Doctor Davis a copy. He recognized the potential importance of the observations and wrote back some opinions that reflected his maturity and wisdom. For one thing, he correctly predicted that the paper would be judged to be so radical and contrary to prevailing opinions that, if it were published at all, it would be only after major and time-consuming editorial reviews and revisions. This proved to be the case. The manuscript sent to *JAMA* was not published until the spring of 1964. Doctor Davis also suggested that the material should be refined, made more highly focused and brought up to date. If these conditions were met, he offered to consider a streamlined version for *SURGERY, GYNECOLOGY AND OBSTETRICS*.

We followed his advice. He published the article in the October 1963 issue of *SURGERY, GYNECOLOGY AND OBSTETRICS*. Its title was "The Reversal of Rejection in Human Renal Homografts with the Subsequent Development of Homograft Tolerance" (8). The other authors were Thomas L. Marchioro, now Professor of Surgery at the University of Washington, Seattle, and William R. Waddell. Three years later, when antilymphocyte globulin (ALG) was introduced clinically as an adjunct to azathioprine and prednisone in what became known as triple drug therapy, the paper was sent to Doctor Davis and was published in *SURGERY, GYNECOLOGY AND OBSTETRICS* (9). Other major developments in immunosuppression in the succeeding years, including the first American trials of cyclosporine and steroids in 1979 and 1980 (10), followed the same publication pathway.

When Doctor Davis died, I had known him for 35 years. After I left Chicago, I wrote or called him several times a year, and until the last two or three years, I always made it a point to meet him at the party given by W. B. Saunders Company at the American College of Surgeons for what for me was an important critique of the past year. As he became old, his attendance there became irregular, but when he did not come, he always wrote and apologized. I did the same. I made no major decision in my professional life without consulting him first. During all this time, I never called him by his first name. It was a matter of respect. To some people who did not know Doctor Davis well, he was a hard and unyielding person. I did not see him that way.

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