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GUEST EDITORIAL

A Transplanter's Credo

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ON November 11, 1990, Stormie Jones died after a brief bout of what initially was thought to be a "flu syndrome." Later, it was realized that she had rejected her heart graft for reasons which are too complicated to summarize here. A memorial service was held on November 29, 1990, at the Children's Hospital of Pittsburgh for Stormie and other medical and surgical patients. For each child, a candle of remembrance was lit. My remarks were as follows:

What Stormie Jones wanted was to be seen and treated like any other child. She might not approve of my saying something extra about her today, without doing the same thing for the others who are remembered here, also with a heavy heart. The special situation is that Stormie came to know everyone, or at least everyone knew her all over the world. She was the beautiful St. Valentine's Day card of February 14, 1984, the six-year-old God-sent child (and there is no other kind) with a name that movie starlets must have envied, a smile which no one who saw it could ever forget, and a courage great enough for five armies. She became a symbol for all those who suffered from heart disease, no matter what their age. At the age of 6, she had become the prisoner of Intensive Care Units because of a kind of heart disease that usually is reserved for old people. She had reached this state because she was born with an inherited cholesterol defect that is reserved for the very young. When she was rescued in 1984 with a heart-liver transplantation, and again last year with a second liver, it brought hope to people of all ages. Along the way, her case established new principles about the intermediary metabolism of cholesterol which were universally applicable. Thus, Stormie's life became a glorious one, and triumphant.

We cannot confer immortality with our feeble efforts to help people. But Stormie did this by herself. The life she had was a full and happy one, filled with more meaning in 13 excitement-filled years than most people could cram into a hundred slow motion years. None of the children who are being remembered today will be forgotten by those who loved them. Perhaps at the head of that band heading toward the stars, can be seen the tow headed happy little 13-year-old girl who will be in the history books long after the rest of us are gone. We wanted more for her, but this was not to be.

The lot of physicians who care for the desperately ill is to reconcile grief with the determination to make things better. Without the sense of personal loss that goes with a dear name and face, there is little progress and no incentive for striving except personal or professional ambition. The field of transplantation is a young one and almost all those who contributed to this new clinical specialty are still alive. At our meetings, they remember what they did or

failed to do by their patients' names, not with numbers or statistics. This is the power of the connection between the doctor and his patient.

It also is the frailty. The cumulative weight of grief can be heavy no matter how few the losses or how frequent the successes which at first were few. At our conferences, the Greek legend is often cited of Icarus who tried to fly in defiance of mortal limitations, but fell when he came so close to the sun that his wax wings melted. This allusion still comes readily to the transplant surgeons who routinely provide treatment that had been considered beyond mortal achievement less than 30 years ago. The burn-out rate was high in the early days of transplantation.

Because of this, and because aging spares no one, only a handful of workers in transplantation (myself included) have stayed in the field continuously throughout its 30-year modern history. We will never forget patients like Stormie Jones or the child, Julie Rodriguez, who in 1967 was the first long survivor after liver transplantation. But it would betray our memory of such patients to use their loss to excuse abandonment of efforts to move ahead. Consequently, my own efforts during the rest of my professional life will continue to be in transplantation.

At the University of Pittsburgh in 1986, a decision was made to strengthen and deepen the institutional commitment to transplantation and programs which relate to it. An interdisciplinary Transplantation Council was formed to facilitate interaction between basic and clinical sciences. Perpetuation of the already large kidney, liver, and heart programs and maintenance of quality control were the primary objectives, but not the only ones. The Council considered and fostered research of all kinds, including organ preservation, histocompatibility typing and matching and, above all, the development of leads for better and safer control of rejection. One product of these efforts was FK 506, a new drug which is envisioned as a means of improving existing services and of achieving a number of previously unattainable objectives, such as intestinal transplantation. The development of FK 506 was made possible by a network of collaborating basic science and

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clinical investigators within and outside the University. These same workers are now screening other new agents and techniques, with sophisticated end points of evaluation that can ensure patient safety when and if the time comes for clinical application.

We realized early on that transplantation research had pervasive applications which go far beyond organ grafting. The linkage which we described more than 20 years ago between the immunosuppression required for transplantation and the development of new malignancies became the focus of a secondary area of investigation, closely tied to the Pittsburgh Cancer Institute. A study of liver growth control factors, which resulted from efforts to define the optimal blood supply of liver grafts also took on a life of its own. These growth factors, which are relevant to cancer research, may also be of importance in promoting the healing of damaged livers, thereby averting the need for transplantation.

Our ultimate goal has been defined with greater clarity during the past 3 decades: the use of transplant-related advances to reduce the need for transplantation may, in the long run, supersede the results of direct transplant applications in numbers and in importance. A significant fraction of patients who need transplantation of the kidney, liver, or heart have had their organs destroyed by so-called autoimmune diseases. In many of these conditions, the disease causing organ destruction has been produced by a distortion or overactivity of the very same immunologic processes which cause graft rejection. Such processes have been controlled or stopped by immunosuppressive agents such as FK 506 and others. The list of these autoimmune diseases is a long one. Aside from those which lead to the destruction of commonly transplanted organs, a number of other medical disorders, such as psoriasis (a skin disorder), regional enteritis (affecting the bowel), rheumatoid arthritis, and multiple sclerosis are also potential candidates for treatment trials with agents such as FK 506. Juvenile diabetes mellitus is another disease which may be controlled, provided that therapy is started during the so-called "honeymoon period," within the first few days after the diagnosis is made. This kind of intervention with FK 506 for patients with recent onset diabetes has been authorized by the US Food and Drug Administration, and was begun in Pittsburgh in November 1990.

Returning to transplantation, the next great surge, already underway with bone marrow, will be with cells (as opposed to whole organ engraftment). Many diseases, and especially those caused by inborn errors of metabolism, may be cured by the less dangerous transfer of cells,

should these techniques be perfected as we anticipate, within the next decade. One immediate example almost one year ago at Pittsburgh, was the first successful instance of pancreatic islet cell transplantation. This previously elusive goal has now been attained at 3 other medical centers. With the use of liver cells instead of a whole liver, Stormie Jones' original disease of hypercholesterolemia might have been treatable—as just one of these examples.

Even cell transplantation, however, cannot be viewed in isolation. Using gene transfer techniques, cells (including cells removed, treated, and returned to the same patient) can be modified in desired ways in order to endow them with the specific functions and characteristics which they are missing, thereby treating a variety of well-defined genetically determined diseases, including inborn errors of metabolism and cancer. This revolutionary approach to gene therapy is a logical outgrowth of the transplantation effort.

The institutional decisions made in Pittsburgh in 1986 subsequently led to my appointment as President of the Transplantation Council, and changed my own professional life. While still a surgeon, my activities have now become focused increasingly on research and development in these many interrelated areas. Between 1986 and today, I first recruited and trained a number of surgical teams with unparalleled technical and management skills who can continue to provide clinical services of the highest order in all components of organ transplantation. We have now institutionalized a surgical program which, at one time, was isolated and highly dependent on very few people. Today, I participate surgically only in cases with unusual problems, or in operations which are not as yet completely worked out. With all of these elements in place, the University of Pittsburgh now has formed a *Transplantation Institute*, which has become my professional home. The cornerstone of the Institute's purpose is to continue the evolutionary process of experimental and clinical organ and cellular transplantation, with all of their ramifications.

There will be a unique opportunity in the decades ahead to justify the major public support, including grant funding for research, without which none of the progress in transplantation of the last 30 years would have been possible. The dividends of the transplantation effort, in terms of its influence on the overall practice of medicine, have greatly exceeded even my own youthful fantasies. It is my hope to continue to participate in the momentum which has now gathered, as we stand on the threshold of the new era in medical therapy which has been heralded by recent advances in organ and cellular transplantation.