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MOST of the surgical specialities can be tracked to the creative vision of a surgeon. Transplantation is an exception. Here, the father of the field is succinctly defined in the dictionary as: "Peter Brian Medawar: a Brazilian born British Zoologist who at the age of 45 shared a 1960 Nobel Prize for his work on acquired immunologic tolerance" (1).

Medawar was mysteriously overwhelming to many colleagues and observers, even when he was young. He was the son of a Lebanese father and an English mother—tall, athletic, abnormally handsome, hypnotically articulate in public, and politely cordial in his personal relations. In September 1969, at the age of 54, he had the first of a series of strokes. These crippled him physically but not in spirit. Although I saw Medawar often professionally and privately over a 22 year period, before and after he was disabled, this sporadic exposure was not enough to understand him. My sense is that no one did, except perhaps Jean, his wife for nearly 50 years.

THE MEANING OF REJECTION

Medawar's dazzling personality before and great courage after his strokes was inspirational, but his fame was based on the unique achievement in 1953 captured by the terse dictionary mention of "acquired immunologic tolerance." The roots leading to this accomplishment had fed on the blood of war. More than 12 years earlier, the recently wed zoologist Medawar—24 years of age and fresh from graduate studies at Oxford University—was assigned to the service of the British surgeon, Dr. Thomas Gibson, to determine if skin allografts could be used to treat casualties from the Battle of Britain.

First, in human studies with Gibson (2), and then with simple and logical rabbit experiments (3), Medawar showed that rejection of the skin was an immunologic phenomenon. This later was shown to be analogous to the cell-mediated de-

layed hypersensitivity that confers immunity to diseases such as tuberculosis (4, 5). The principal evidence in the early studies was that repetitive grafts from the same donor were rejected more rapidly with each successive attempt—the sensitization and donor specificity confirming an earlier clinical observations by Emil Holman of Stanford in skin-grafted burn victims (6).

Once it was established that rejection was an immune reaction, strategies began to evolve to weaken the recipient immune system. By 1953, total body irradiation (7) and adrenal cortical steroids (8, 9) had been shown to delay skin rejection. However, this immunosuppressive effect was either minor if the animals survived, or lethal to the recipient if the grafts were spared. There was no margin of safety.

THE BOMBSHELL PAPER

In the resulting atmosphere of nihilism about clinical applications, a three and one-half page article by Billingham, Brent, and Medawar in the October 3, 1953 issue of *Nature* describing acquired tolerance (10), came as a blinding beacon of hope. The three men had learned that donor splenocytes could be engrafted by their intravenous infusion into immunologically immature mice *in utero* or perinatally. When these inoculated recipients matured, they could accept skin and other tissues from the donor (but from no other) mouse strain.

The immune system of the recipients had been populated by the immunocytes of the donor, meaning that they were now chimeras. The race was on to convert this principle to humans. However, the dark side of their accomplishment soon was revealed by the two younger members of Medawar's team, Billingham and Brent (11) and by the Dane, Simonsen (12). The engrafted donor cells could turn the tables and reject the defenseless recipient unless the tissue match was a good one. This was the dreaded graft versus host disease (GVHD) in which transplanted donor cells attacked the recipient skin, gastrointestinal tract, lungs, liver, and the bone marrow itself. Medawar's dream of 1953 was suddenly a nightmare. Or was it?

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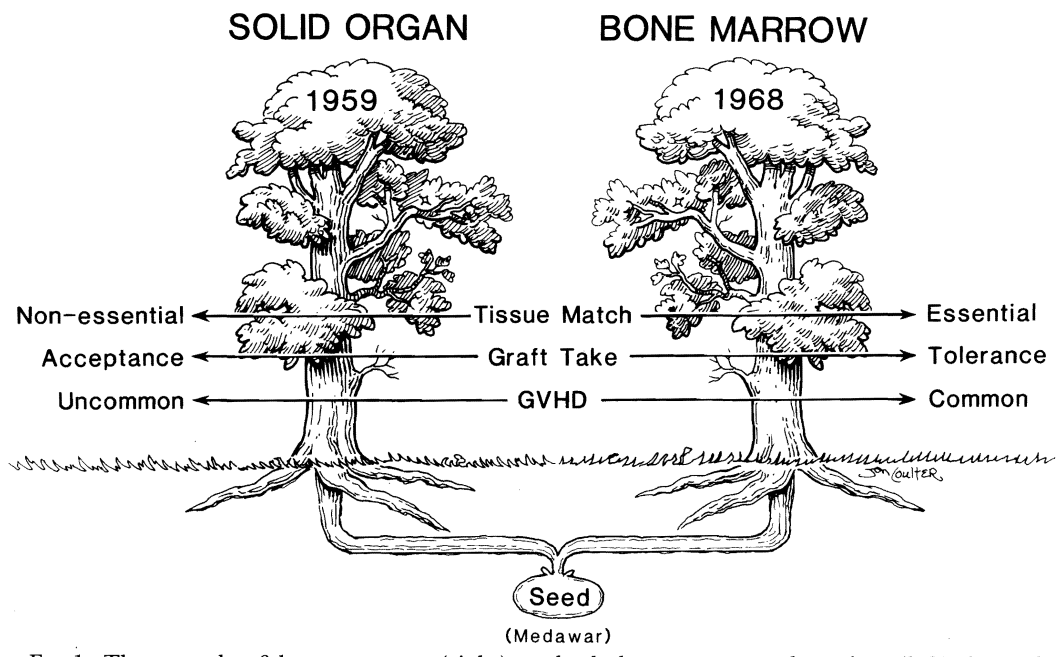


FIG. 1. The growth of bone marrow (right) and whole organ transplantation (left) from the seed planted by Peter Medawar during World War II. GVHD, Graft versus host disease.

CLINICAL BONE MARROW TRANSPLANTATION

On the contrary, the work took a straight line to clinical application (Fig. 1), after the dem-

onstration by Prehn and Main (13) that similar tolerance could be induced in adult mice rendered immunologically defenseless by total body

Two-Way Paradigm (Organ)

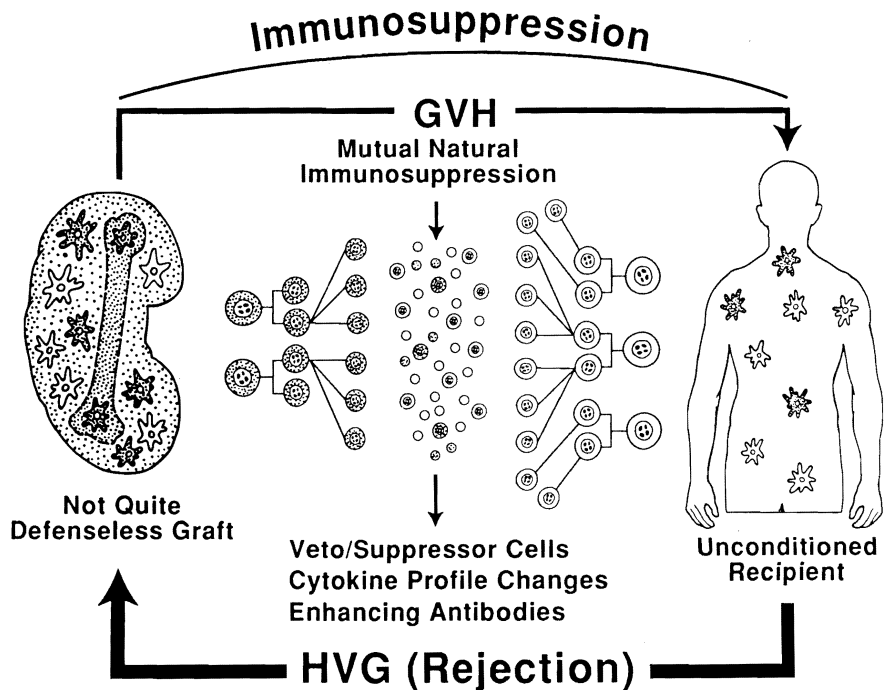


FIG. 2. Bidirectional mechanism of whole organ graft acceptance involving a graft-versus-host (GVH) reaction by the bone marrow-derived donor leukocytes in the graft that are pitted against the whole recipient immunologic apparatus (host-versus-graft [HVG], rejection). For conventional whole organ clinical transplantation, the recipient is not preconditioned.

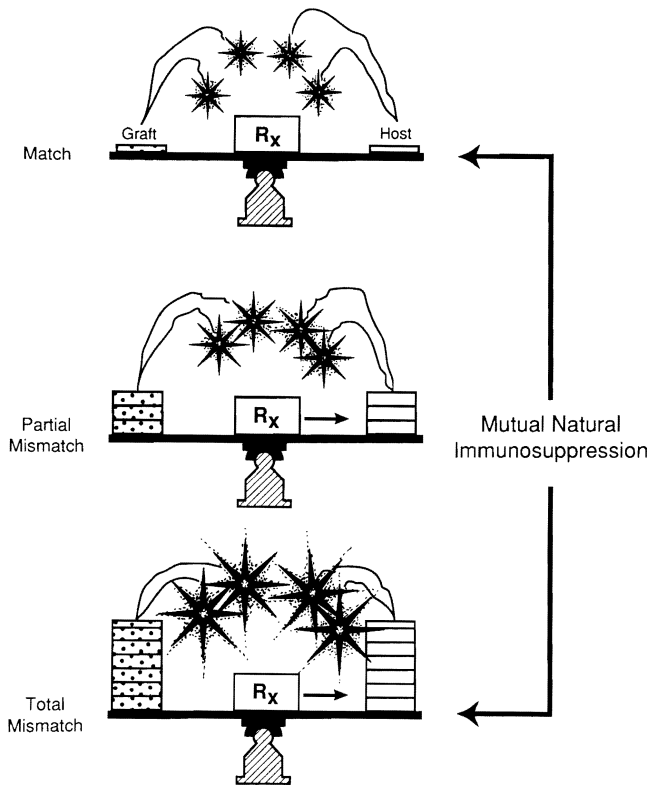


FIG. 3. Explanation with the two-way paradigm (Fig. 2) for the poor prediction by tissue matching (HLA) of outcome after whole organ transplantation. Rx, Treatment.

irradiation before splenocyte (or later bone marrow) infusion. The recipient conditioning, known as cytoablation, also could be accomplished with myelotoxic drugs. However, as Billingham, Brent, and Medawar had predicted (5), donor specific tolerance could be induced in humans without GVHD only if there was a good tissue (HLA) match. In 1968, 15 years after the epic Billingham, Brent and Medawar publication (10), Robert Good

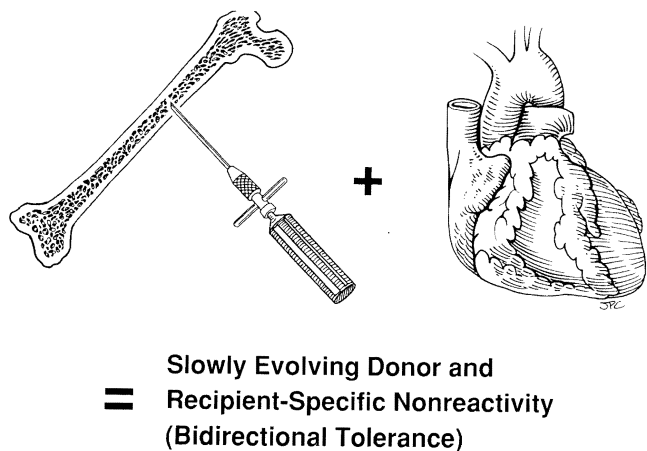


FIG. 4. Strategy for donor leukocyte augmentation in recipients of whole organ allografts. The bone marrow is given at the time of the operative transplant procedure.

(14) and Fritz Bach (15) reported the first two successful human bone marrow transplants. Both recipients of well matched bone marrow from blood relatives are still alive. This was a triumph in which the principal clinicians were internists, as summarized 25 years later in the acceptance speech by the 1990 Nobel Laureate Donnall Thomas (16).

CLINICAL WHOLE ORGAN TRANSPLANTATION

Surgeons pursued a quite different pathway. Rejection of whole organs was at first construed as a mirror image of the Billingham-Brent-Medawar model in that the leukocyte villains were the recipient rather than the donor immunocytes, and the defenseless allografts were the victims instead of the instruments of rejection. Literally accepted, this “one-way paradigm” provided no hope that whole organ transplantation would be feasible without first exchanging the bone marrow with that of the donor along the lines of the internist strategy described above.

Despite the consequent pessimistic predictions, Nobel Laureate Joseph Murray of Boston showed in January 1959 that renal transplantation was feasible—after sublethal total body irradiation of a fraternal twin recipient, but without the donor bone marrow (17). Five more examples of long survival (two with unrelated kidney donors) was reported in Paris during the next three years on the services of Jean Hamburger (18) and Rene Kuss (19).

This looked like a different tree from Medawar’s original seed (Fig. 1), in which success was called graft acceptance (not tolerance), was not dependent on good tissue matching, and did not have a threat of GVHD. Then, Murray and associates (20) showed that the same thing could be accomplished in humans pharmacologically, using chronic therapy with azathioprine. This observation came after extensive preclinical studies in dogs with Murray’s young associate, Sir Roy Calne of England, at the forefront (21).

The clinical results with azathioprine were poor at first, no better than with total body irradiation (22). However, this changed dramatically in 1962 when azathioprine was systematically combined with prednisone at the University of Colorado (22).

Rejection that developed despite azathioprine treatment could be reversed surprisingly easily with prednisone. More importantly, the subsequent need for maintenance immunosuppression with both drugs frequently declined. The

same characteristic cycle of immunologic confrontation and resolution was soon observed with the liver (23), ultimately with all other transplanted whole organs, and with each of the increasingly potent new drugs introduced during the next 30 years. This reproducible chain of events constituted the cardinal principle on which the new and increasingly practical field of transplantation was based. Something had changed in the host, the graft, or both. But what?

THE MEANING OF ORGAN "ACCEPTANCE"

Medawar was perplexed. In 1964, commenting on the surprisingly good results of renal transplantation using azathioprine and prednisone in the Colorado series, and in the Richmond, Virginia, series of David Hume, Medawar wrote, ". . . foreign kidneys do sometimes become acceptable to their hosts for a reason other than acquired tolerance in a technical sense . . ." (24). As usual, his insight was uncanny.

Nevertheless, 30 years and a revolution in immunology elapsed before the mystery of whole organ graft acceptance was resolved by study of the still-surviving early Colorado kidney and liver recipients. Donor leukocytes of bone marrow origin, which are part of the structure of all organ grafts (the so-called "passenger leukocytes"), had migrated from the transplanted organs and were found in the skin, lymph nodes, blood—everywhere throughout the recipients—as many as 30 years later (25, 26).

In essence, a small fragment of disseminated extramedullary donor bone marrow (illustrated schematically in Figure 2 as a bone silhouette) had become assimilated into the overwhelmingly larger immunologic network of the host. Whole organ transplantation involved a mutually canceling graft versus host as well as host versus graft reaction, with the ultimate development of reciprocal immunologic nonreactivity of both populations. The two components of transplantation immunology originally defined separately by Medawar and his colleagues, at long last, had been joined. The secret was that they were interactive.

MILESTONES AND ENIGMAS REVISITED

The two-way cancellation effect, illustrated in Figure 3 as a teeter-totter, explained how the tissue matching influence was blindfolded and rendered nonpredictive with whole organ transplantation, explained the characteristic cycle of

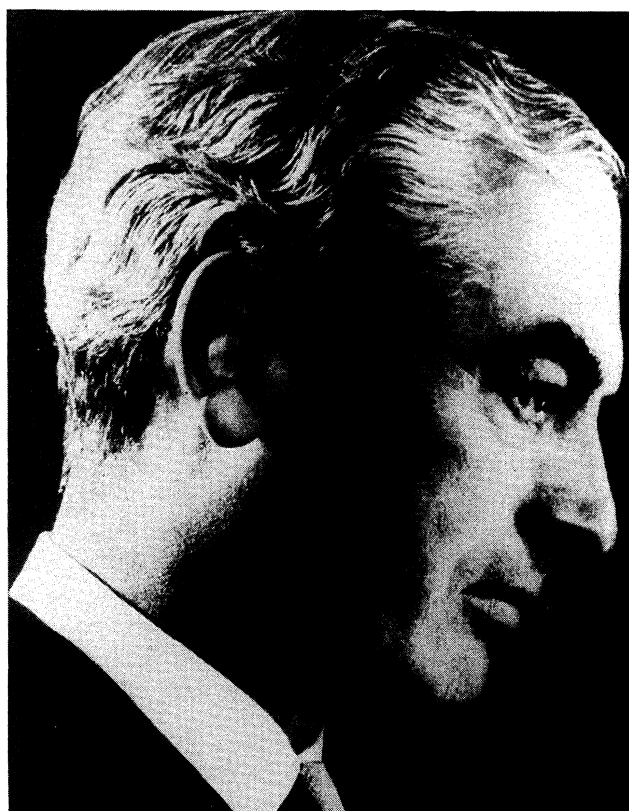


FIG. 5. Peter Brian Medawar (1915-1987).

crisis and recovery that we see in our patients postoperatively, and made it understandable why GVHD usually does not occur after liver, intestinal, multivisceral, and heart and lung transplantation. It also explained why all whole organs have the inherent capability of tolerance induction. This had long been a contention of Paul Russell (27), the first American surgeon to work with Medawar.

In closing the once vast gap between the bone marrow and whole organ transplantation fields, the two-way paradigm of transplantation immunology developed in 1992 (25) also had exposed a perioperative window of opportunity, during which unaltered HLA mismatched bone marrow can be given safely to whole organ recipients without recipient cytoablation or any deviation from the standard immunosuppressive strategies developed empirically 30 years earlier (Fig. 4). During the last 2 years, gross chimerism has thereby been produced routinely (28)—in the first cohort of patients to undergo HLA mismatched whole organ transplantation with the reasonable prospect of eventually becoming drug free. This, of course, was the final fulfillment of Medawar's dream. It came five years after his death in 1987 at the age of 72 years.

A MEDICAL GALILEO

At the Transplantation Society Congress in Paris in 1992, I noted that almost 400 years to the day previously Galileo had arrived to his faculty position at the University of Padua. With a telescope constructed by himself, he began the inquiries that defined the mysterious universe and resulted in man walking on the moon. Our Galileo was Peter Medawar, whose first probes into the biologic meaning of rejection and the universe of transplantation took place about 14 percent of the time from now, back to those medieval days.

Armed with dissecting scissors, a few rabbits and mice in a dilapidated London laboratory—and a remarkable brain that stayed vital even as its motor function was cruelly removed piecemeal—this zoologist founded a new field that crossed all specialty barriers and blurred, as no one ever had before, the distinction between basic and clinical science. Small wonder that we remember so vividly and fondly the proud face illustrated in Figure 5.

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