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HENRY SHERWOOD LAWRENCE
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A Biographical Memoir by
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Biographical Memoir

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H.S. Lawrence

HENRY SHERWOOD LAWRENCE

September 22, 1916–April 5, 2004

BY SALAH AL-ASKARI

HENRY SHERWOOD LAWRENCE WAS A distinguished physician, a master teacher, and a pioneer in research on cell-mediated immunity. At a time when scientists focused on the more popular study of humeral immunity and the nature of immunoglobulins in experimental animals, Lawrence emphasized the role of cellular immunity in human responses to disease and antigenic agents. Utilizing man as his study model he discovered that lymphocytes from sensitive individuals produce an active product, “transfer factor,” that played a major role in cellular immunity. He was a highly regarded clinician with a special expertise in infectious diseases, and a dedicated teacher and role model for students, residents, fellows, and young physicians.

Lawrence, known to his friends and colleagues as either Sherwood or Jerry, was born on September 22, 1916, in Astoria, New York. His father, Victor John Lawrence, was a Pennsylvania Railroad man and his mother, Agnes Whalen, was a homemaker.

Lawrence attended Public School 6 in Astoria and Townsend Harris High School and then transferred to the prestigious Stuyvesant High School in New York City, where he became interested in biology. On the advice of his biology teacher he enrolled in New York University at “the Heights.”

Upon the death of his father in 1937, Lawrence, while he was in his third year of college, became the sole supporter of his mother and of several cousins whose fathers were out of work during the Depression. He had to transfer to the New York University campus at Washington Square in order to complete his studies at the night school. Always personally fastidious and a sharp dresser, he had no time to change after work and attended classes in his work clothes. His day job was with the Pennsylvania Railroad at their Sunnyside rail yard in New York as a straw boss, an assistant foreman of a work gang. He rejected a position as clerk typist, as it paid \$5 less per week. His resolve to find a way out of Sunnyside never faltered.

In 1938 Lawrence was accepted into the School of Medicine at New York University and was offered a scholarship of \$200 per annum. He informed the school representative that he needed a full scholarship or he would not be able to attend. He left the meeting feeling his life's dream fading. Fortunately, his mother came to the rescue; she sold her life insurance policies and covered the difference. This gift was the beginning of a lifelong devotion to his students, residents, young physicians, and patients at "his hospital," Bellevue.

At medical school Lawrence was one of the poor boys who brought their lunch from home to eat under the pipes in the basement of the old Bellevue Hospital. During medical school he became a very good friend of Winthrop ("Win") Sands, who had sold his seat on the New York Stock Exchange and had begun a career in medicine. This was a friendship that changed Lawrence's life.

On December 8, 1941, Lawrence enlisted in the navy, but he had to sign a waiver stating that because he was 27 pounds underweight, the navy would not be responsible for any illness he incurred while in the service.

At the end of the academic year 1941 Sands casually asked Lawrence about his summer plans. He was stunned to learn that Lawrence would be spending the summer unloading freight cars at Sunnyside rail yard. Sands, as Jerry said in later years, became "the founder of this feast" by secretly arranging a job for Lawrence through Sands's banker and guaranteeing him a salary of \$40 a week. Lawrence did not find out about this until years later when his wife, Dorothea, told him that she had discovered the correspondence between Sands and his banker while clearing out the desk of her boss, who was the manager of the United China Relief Campaign.

Lawrence met his wife, then Dorothea Wetherbee, while she was working in the accounting department of the United China Relief Campaign. One morning her boss said, "Miss Wetherbee, this is Mr. Lawrence. Please show him how to use the adding machine." Soon they were dating and eventually they married at the chapel of Bellevue Hospital on November 13, 1943. It was the beginning of a long and happy life. Dorothea summed up their mutual feeling by saying, "He was the nicest man I ever met."

After graduating from medical school in 1943 Lawrence served as an intern, 3rd division Medicine at Bellevue Hospital with an annual salary of \$216. Win Sands advised him to buy his navy uniform from Brooks Brothers, a high-class store, saying ever cheerfully that if Lawrence had to die at least he would die dressed like a gentleman.

After completing his internship Lawrence was on active duty from 1944 until 1946 in the U.S. Navy and attained the rank of lieutenant, senior grade, Medical Corps. He was in the Amphibious Service on landing ship tanks (LST), and participated in the invasions of Normandy, Southern France, Okinawa, and the Philippines. After unloading, the LST would be transformed into a hospital ship and part of the tank deck

would become the operating room where Lawrence treated the wounded. He was awarded the Bronze Star and other citations for his services. In later years he would suddenly become sad at the thought of “all the boys I could not save, the boys I had to leave at the beaches.” The abrupt end of the war spared him a fifth invasion—Japan.

With the war won Lawrence was assigned to Pier 96 Naval Station on the Hudson River in New York. Following his discharge from the Navy in 1946 he began his residency training as an assistant resident in internal medicine at Bellevue—without compensation.

In 1946 his first child, Dorothea Wetherbee Lawrence, was born, followed soon after by Victor John and Geoffrey Douglas.

After completing his residency training Lawrence was appointed as the John Wyckoff Fellow in Medicine (1948-1949). During his early years he became very good friends with his mentor, Alvin M. Pappenheimer, whose help and encouragement were unflinching.

The discovery of cellular transfer of delayed-type hypersensitivity (DTH) in guinea pigs by K. Landsteiner and M. W. Chase had a special affect on Lawrence’s interest in immunity. His early studies in human subjects involved the transfer of DTH to tuberculin with viable blood leukocytes (WBC) from sensitive subjects. This was a specific and durable transfer of DTH to nonimmune recipients. It is of interest that during his early work with William S. Tillett, chair of the Department of Medicine while Lawrence was the John Wyckoff Fellow, he had only a bench space in the hospital ward’s routine laboratory. His only equipment—tuberculin syringes, needles, vials of PPD, a glass jar with cotton pledgets in alcohol, and a brass syringe container that could be sterilized in the ward sterilizer—was kept in the bottom drawer (the one with the lock) of Clair Gautier’s desk. Ms. Gautier

was the clerk who typed the discharge summaries for the house staff. The meager pay from the fellowship and a small income from working as the director of the Student Health Office were all that sustained Lawrence and his family for several years.

Lawrence's early studies showed that (4.2×10^6) viable WBC from donors with marked cutaneous sensitivity to tuberculin failed to transfer the sensitivity to tuberculin-negative recipients. However, (85×10^6) WBC from such donors consistently transferred the sensitivity. Controls showed that (170×10^6) WBC from tuberculin negative donors did not confer tuberculin sensitivity to tuberculin-negative recipients. This was also observed in the transfer of DTH to streptococcal M-substance. Only WBC from donors with DTH to streptococcal M-substance was capable of transferring the reactivity to negative recipients.

Lawrence's studies on DTH confirmed the observations of Landsteiner and Chase. However, in their studies Landsteiner and Chase utilized pooled cells from 5-7 sensitive guinea pigs to sensitize one animal, and the transferred sensitivity lasted only for a short period, 5-7 days.

After his success in transferring DTH with live WBC, Lawrence proceeded to use disrupted WBC to transfer DTH to tuberculin and streptococcal M-substance. The cells were disrupted either by lysis, following incubation in distilled water at 37°C for 4-6 hours, or by 7-10 cycles of freezing (with dry ice alcohol mixture) then thawing at 37°C . He found that WBC extracts from sensitive donors successfully transferred DTH to tuberculin, streptococcal M-substance, and diphtheria toxoid to the antigen-negative recipients. For convenience he labeled this moiety "transfer factor" (TF).

Together with Felix Rapaport, Lawrence used the transfer of DTH to coccidioidin to determine whether the passive

transfer of DTH conferred *de novo* reactivity to the recipient or whether it was merely boosting subliminal response already present. They found that DNase-treated WBC extracts from individuals in California who were coccidioidin sensitive successfully transferred the reactivity to East Coast recipients who were never exposed to that antigen (as the fungus does not exist in the East), thus proving that the DTH was passively transferred to the antigen-negative recipients.

To eliminate the role of DNA and RNA in the transfer of DTH, leukocyte extracts from sensitive donors were treated with RNase, DNase, or trypsin. The results showed that such treatment did not affect the capacity of the cell extract to transfer DTH to the antigen-negative recipient.

In other studies Lawrence and Pappenheimer used WBC extracts from SK-SD sensitive donors to transfer DTH to diphtheria toxoid. They found that such extracts transferred DTH to the toxoid, but unlike the case in naturally sensitive individuals there was no transfer of either primary or secondary antibody response to the toxoid. Lawrence also showed that DNase treated WBC from coccidioidin-sensitive donors transferred only DTH to coccidioidin but not the complement-fixing antibody response to coccidioidin. The failure of TF to transfer antibody forming capacity was also confirmed by other investigators. These observations ruled out the possibility that TF acts as a superantigen.

In two elegant experiments Lawrence attempted to determine whether the recipient of TF replicates the active moiety or whether it is merely a signal to activate a change in the recipient's system. He used disrupted WBC from donors with DTH to tuberculin and streptococcal M-substance to transfer DTH to a negative recipient A, and then used disrupted WBC from Recipient A to transfer the acquired DTH to recipient B. The results showed that recipients A

and B exhibited strong DTH to tuberculin and streptococcal M-substance, which argued against the notion that TF is a super antigen and lent credence to the concept that a new population of cells arise in recipients of TF and that such cells can transfer the acquired DTH to other negative recipients.

Having established the transfer of DTH to tuberculin, fungus, and bacterial toxin, Lawrence turned his attention to the study of allograft immunity in man. Working with Felix Rapaport and J. M. Converse, the head of plastic and reconstructive surgery at New York University, Lawrence demonstrated that WBC extracts, TF, from human subjects hypersensitized by multiple skin allografts were capable of transferring the specific immunity to HL-A antigens to unrelated individuals. They observed that the recipients of WBC extracts rejected skin allografts from the immunizing donors in an accelerated fashion. These studies established the existence of TF in transplantation immunity and attracted the attention of the leading scientists in the field, like Jean Dausset and Sir Peter Medawar, who later won a Nobel Prize.

Lawrence had a special relationship with Sir Peter Medawar and wrote the following in one of his speeches:

“I first met Peter at a New York Academy of Science symposium in the early 50’s. We had each presented data to support the notion that homograft rejection occurred via a cellular mechanism without, as Peter suggested, the intercession of antibody. In polite immunological circles of the time, an immunological transaction in the absence of antibody was an aberrant idea that would soon succumb to the weight of data. We were each delighted to meet a kindred spirit and became fast friends from then onwards.”

That incident led to the appointment of Lawrence in 1959 as a Commonwealth Foundation Fellow to work with Sir Peter Medawar in England and was followed by many visits

by Lawrence or Medawar to the other's laboratories. The following excerpt from a letter that Medawar sent to Lawrence demonstrates his appreciation of Lawrence's work:

I admire your work enormously and the way you have always gone about it. Not many people would have persevered as you have done with such an enormously difficult task to work out the mode of action with transfer factor using clinical materials only.

With the existence of TF documented by many investigators, Lawrence proceeded to purify and characterize it. He and his colleagues showed that TF can pass through Visking cellulose dialysis membrane and that the dialysate could be concentrated by lyophilization. The lyophilized powder was active for five years at 4°C. In these studies 4 ml of DNase-treated, frozen and thawed WBC extracts were dialyzed against an equal volume of distilled water for 18 hours in a cold room and then lyophilized. The lyophilized powder was reconstituted to its original volume with distilled water and passed through a Swinney or Millipore filter prior to its injection into the negative recipient. Such reconstituted lyophilized dialysates conferred tuberculin and coccidioidin sensitivity to the negative recipients. The integrity of the dialysis sacs were tested by adding Benes-Jones protein or papain-digested Y-globulin fragments to the sac's contents, and then testing for them in the dialysates. Neither the Y-globulin fragments nor any protein were detected in the dialysates. The potency of the dialysate preparations was increased by increasing the ratio of the dialysant to the dialysate to 1:50. This was shown by the increased intensity of DTH to coccidioidin in the negative recipients. Further purification of transfer factor was achieved by passing the reconstituted lyophilized dialysate through Sephadex G-25 columns. Fractions collected under peak II (molecular weight <10,000) transferred DTH to coccidioidin in negative individuals, indicating that the

active moiety in transfer factor is likely to be a small polypeptide-polynucleotide. This observation was confirmed by other investigators.

The lack of an animal model for the *in vivo* characterization of TF made Lawrence turn his attention to the *in vitro* study of cellular immunity. In their studies of DTH in guinea pigs, M. George and J. H. Vaughan used the migration of peritoneal macrophages from capillary tubes in small culture chambers. They observed inhibition of migration of macrophages from tuberculin-sensitive guinea pigs when PPD was added to the culture chambers. However, they had difficulty with their technique, because their macrophage preparations were contaminated with red blood cells. Lewis Thomas, who had visited their laboratory, was impressed by their approach. He suggested to Lawrence that John David and I (fellows in the lab) try it. I reproduced the culture chambers in my basement workshop and I was able to obtain blood-free, mineral-oil-induced peritoneal macrophages by not feeding the test animals for 24 hours and exanguinating them prior to harvesting the peritoneal macrophages. After David and I confirmed the observations of George and Vaughan, Thomas informed them of our technical improvement and insisted that they publish their paper first.

David subsequently discovered that the inhibition of macrophage migration was due to the production of a heat-stable, nondialysable protein by lymphocytes from guinea pigs with DTH when they are exposed to the specific antigen. He labeled this moiety "migration inhibitory factor" (MIF). In subsequent studies we also observed inhibition of migration of peritoneal macrophages from guinea pigs sensitized with multiple skin allografts when mixed with sessile lymphoid cells from the sensitizing donors. Lymphocytes from other animals did not affect the migration of the sensitive cells.

Similar results were obtained in inbred strains of mice. These observations indicated that the inhibition of macrophage migration from animals exhibiting allograft sensitivity by the specific histocompatibility antigens is an *in vitro* correlate for transplantation immunity.

In collaboration with D. C. Dumonde, a newly arrived fellow from the Mill Hill Institute in London, we found that spleen microsomes function as histocompatibility antigens when administered by the intradermal or the intraperitoneal routes. We also found that supernatants from cultures of sensitive lymphocytes plus donor antigens, lymphocytes, or spleen microsomes inhibited the migration of peritoneal macrophages from normal animals, indicating the production of MIF by sensitive lymphocytes upon exposure to the specific sensitizing histocompatibility antigens. It also demonstrated the nonspecific action of MIF in transplantation immunity. These findings were similar to the *in vitro* observation on classic DTH models, suggesting a common mechanism.

W. Borkowsky and other investigators found that TF (or dialyzable leukocyte extract, DLE) contained a small (<10K but >3.5 K) peptide with a blocked N-terminus that originated from CD4 T-helper cells and could bind to CD8 T-cells and to antibodies directed at MHC class II antigens. It could also bind to the antigen for which it demonstrated specificity and to antibodies directed at anti-VH regions. In the course of this work it was shown that in addition to a TF which would deliver instant CMI to a specific antigen, there was also a TF (or DLE) which could abrogate antigen-specific CMI. This "suppressor TF" originated from immune CD8 T-cells and could bind to CD4 T-cells, as well as anti-MHC II and anti-VL antibodies. It could also bind to antibodies directed at the antigen that was the target of the cellular immune response. This sort of information suggested that TF acted in a sort of idiotypic/anti-idiotypic network of immunity.

Lawrence and F. T. Valentine used thymidine incorporation to further characterize the *in vitro* action of TF. They found significant increase in thymidine incorporation when tuberculin-sensitive lymphocytes were cultured in the presence of PPD. In addition, when supernatants from such cultures were added to cultures of tuberculin-negative lymphocytes, there was also a significant increase in thymidine incorporation. The active moiety in the supernatant was nondialyzable, antigen-dose dependant and could not be sedimented at 100,000 g. They named it lymphocyte transforming factor (LTF).

The ability of TF to confer instant CMI provoked many immunologists to use TF to treat diseases ranging from chronic infectious diseases to congenital immunodeficiency and even malignancies. Reports of cure of chronic mucocutaneous candidiasis, Wiscott-Aldrich syndrome, generalized vaccinia, disseminated fungal infections, and leprosy appeared in many journals and generated great interest in TF. Nevertheless, it must be admitted that TF does not seem to relate to any of the known soluble immune mediators, and its nature remains a fascinating but obscure puzzle.

To explain the role of TF in immunological homeostasis Lawrence proposed, in 1959, the self+x hypothesis as the *modus operandi* in CMI. He postulated that foreign antigens (bacterial, viral, fungal, and other nonself components) ingested by macrophages caused alterations in the self antigens on host cell surfaces self+x. Ingestion of such cells by other reticuloendothelial cells stimulated the production of TF against the self+x complex. It seems that Lawrence had anticipated the findings of Doherty and Zinkernagle (i.e., antigenic recognition in the context of self major histocompatibility antigens).

Lawrence's contributions to the understanding of DTH were documented in his publication of over 180 articles,

books, and chapters in books. The following is a poem by Lewis Thomas written in honor of Jerry's birthday in 1979. It reflects his appreciation of Jerry's professional achievements.

In glass and in life
Investigations are rife.

This year has been great
For TF we can state,
Has all critics tamed,
At least as of late.

Lawrence has shown
It was specific in man.

Demonstrate that they can
Cause specific inhibition
Of cells wandering condition.

To this one might say
"Why isn't that nice"
But for immunological skeptics
It works even in mice.

A good year for TF,
And for you too, Jerry
We hope that your birthday
Proved to be merry.

As a clinician Jerry was highly regarded as an expert in infectious diseases and as a unique role model in bedside manners. He always emphasized a humanitarian, compassionate, and respectful approach in patient management.

During his tenure at New York University Medical Center he served as an attending physician at University Hospital, Bellevue Hospital, and Manhattan Veterans Administration

Hospital. He was also head of the Infectious Diseases and Immunology Division from 1959 to 2000, codirector of medical services from 1964 to 2000, director of the Cancer Center from 1974 to 1979, and director of the AIDS Research Center from 1989 to 1994.

Lawrence's contributions and discoveries earned him honors and recognition at home and abroad. He was elected to numerous distinguished societies as a member, charter member, or honorary member. These included the American Association of Immunologists, Society of Experimental Biology and Medicine, Harvey Society, Infectious Disease Society, Peripatetic Clinical Society, Interurban Clinical Club, American Academy of Allergy, Transplantation Society, American College of Physicians, Royal Society of Medicine (England), Royal College of Physicians and Surgeons (Glasgow), and the Société Française d'Allergie (France). He was an invited lecturer to the Société Française d'Immunologie (Institute Pasteur). He was elected to membership in the National Academy of Sciences in 1972.

He was also appointed consultant to or chairman of many prestigious scientific councils, including the American Thoracic Society; Health Research Council (City of New York); Armed Forces Epidemiological Board, Streptococcal and Staphylococcal Commission; National Institute of Health, Institute of Allergy and Infectious Diseases, Allergy and Immunology Study Section; American Rheumatism Association; and the National Research Council (member, Committee on Cutaneous System and chair of the Committee on Transplantation).

Lawrence served on many editorial boards for scientific journals, including *Transplantation*, *Proceedings of the Society of Experimental Biology and Medicine*, and *Annals of Internal Medicine*. He was the founder and editor in chief of *Cellular Immunology*.

Lawrence received many awards and prizes for his contributions, including the von Pirquet Gold Medal for Scientific Advancement in Immunology from the Forum on Allergy; the New York Academy of Medicine Medal for Outstanding Contributions to Science; the American College of Physicians Award for Outstanding Contributions to Science; the Lila Gruber Award for Cancer Research from the American Academy of Dermatology; and the Distinguished Teacher's Award from the New York University School of Medicine. In 1979 he was named the Jeffrey Bergstein Professor of Medicine at New York University.

Lawrence was a gracious, humble, and modest man who treated others with respect and dignity regardless of their position in society. He was a man of honor who loved family and friends. Never forgetting his roots, he loved the work of Charles Dickens, because the people he met in the wards of Bellevue Hospital were the kind of people about whom Dickens wrote. He was so taken with his British experience after his visits with Medawar that he adopted some continental habits, such as afternoon breaks. He preferred English tweed, ascots, bow ties, Irish doc caps, shirts with French cuffs, and odd jackets with nipped waists and side vents. His office was decorated with a segment of the Bayeux Tapestry, a gift from his wife, Dorothea, showing the embarkation of William the Conqueror from a point not far from where Jerry's LST had landed on D-Day. When asked about it, Jerry would say that he was "the last of the Plantagenets." His remarkable resemblance to Alec Guinness was so striking that a birthday gift from his laboratory staff was a poster of the Star Wars character Obi-Wan Kenobi. People often joked that they might be twins separated at birth.

I met Jerry when I had just finished my training in urology and was interested in kidney transplantation. It was my privilege to be Jerry's first research fellow after his return

from his fellowship in England. I was followed by B. Zweiman, John David, D. C. Dumonde, F. T. Valentine, R. S. Holzman, W. Borkowsky, and many others.

Jerry was especially kind to young researchers and was keenly interested in training, mentoring and advancing the careers of those who worked with him. He took his research fellows to exclusive meetings and conferences, such as those of the Streptococcal Commission of the Armed Forces Epidemiological Board and the National Academy of Sciences. To advance their careers he would introduce his fellows to leading scientists during the meetings. He was very tolerant and never angry. When it was time to publish the discovery of MIF he insisted that John David should take the credit by publishing it alone, a very noble and generous act. Lawrence's laboratory needed a lot of equipment. John David and I would go with him to the meetings of the Federation of the Society of Experimental Biology and Medicine and shop at the exhibits like children at an FAO Schwartz toy store.

He taught his fellows how to write scientific papers and grant applications and how to utilize the subtleties of the English language. He stressed the use of the passive voice when deemphasizing a controversial point.

Jerry was very tolerant of the families and children of his fellows. Robert Holzman recalls that he used to bring his son, Dan, to the laboratory on Saturdays. Dan always remembered Dr. Lawrence as "the man who was in the laboratory on Saturdays," and on hearing of his passing, wrote a full page memoir in his blog.

Jerry was a loving and devoted father. His daughter, Dorothea, remembers that he allowed his children to have their own voice—he was never opinionated or authoritarian—and he seemed genuinely eager to listen to them, even when they were quite young. He was a devoted husband and hated to be away from his beloved wife, Dorothea ("Dot").

On one occasion he was going to stay in Paris for one week after his talk at the Pasteur Institute. However, he surprised his family when he returned the next day after giving his talk. He simply missed them too much to stay away. He brought Dot flowers several times a week and regularly left her love notes all around the house. His down-to-earth attitude was exemplified in the statement of an African American elevator operator at Bellevue to Jerry's son Geoffrey: "You know, son, your father is a great man. I've been told that he is a good physician, and he's starting to be recognized for his research. Your father never failed to speak to me—many of these doctors I knew when they were students and most do not even look at me—cause they are too important now."

Unfortunately, Jerry suffered a serious accident, which forced his retirement in 2000 and lead to his death in 2004. He will always be remembered as a member of what Tom Brokaw called "the greatest generation."

I AM INDEBTED TO THE Lawrence family in compiling the history for Jerry's story. The contributions of Drs. John David, William Borkowsky, and Robert Holzman were invaluable in the preparation of this memoir.

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