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The Paediatric Cardiology Hall of Fame

Abraham Morris Rudolph

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In the words of Dr William Friedman, who delivered the tribute when Dr Rudolph recently received the St. Geme award, Abe Rudolph is *the* leading figure in academic pediatric cardiology. The evaluation of Abe by Dr Julius Comroe listed this citation: "Wherever I have been in the United States or in foreign countries, Dr Rudolph is always listed as the number one Pediatric Cardiologist." When Abe was being recruited to the University of California, San Francisco, Dr Alex Nadas wrote the following recommendation "I have known Dr Rudolph for over 15 years. I have watched him grow, develop and reach his full potential. Unquestionably he is *the* outstanding investigator in Pediatric Cardiology in the United States. In addition he is a superb clinician, as well as a good teacher."

Abe has received numerous awards for his intellect and his science, has spawned another generation of outstanding individuals in disciplines from cardiology to cardiovascular science and fetal medicine, and has published prodigiously. He has received many honors, including the E. Mead Johnson and Borden Awards for Research in Pediatrics, the Research Achievement Award of the American Heart Association, the Lifetime Achievement Award of the American Academy of Pediatrics, the Joseph St. Geme Leadership Award of the Federation of Pediatric Societies, the Howland award of the American Pediatric Society, the Arvo Yllpo Award in Helsinki, Finland, and the Jonxis Medal in Groningen, Holland. He is a member of the Institute of Medicine of the National Academy of Sciences, and a former President of the American Pediatric Society. In 1996, he received the Dokteur Honoris Causa Degree from the Rene Descartes University at the Sorbonne in Paris. In 1999 he received the Nils Rosen von Rosenstein Award from Uppsala University, Sweden. In 2000, he was elected a Fellow of the American Association for the Advancement of Science.

He has published 318 manuscripts in peer-reviewed journals, made 85 invited contributions, book chapters or conference reports, and written or edited 9 books, including the latest, a second edition of *Congenital Diseases of the Heart* unofficially subtitled "The Little Red Book of Chairman Abe". He has edited, in conjunction with Julien Hoffman, and now his son, Colin, one of the most widely read pediatric texts, *Rudolph's Pediatrics.*

He was the first chief of cardiac catheterization at The Children's Hospital in Boston, and became the Chief of Pediatric Cardiology at the Albert Einstein College of Medicine in New York. Then, at the University of California in San Francisco, he was appointed Professor of Pediatrics, Director of Pediatric Cardiology, and a Senior Staff Member of the Cardiovascular Research Institute. He held the chair of Neider Professor of Pediatric Cardiology, and was a Professor of Physiology and Obstetrics and Gynecology. In 1986, he was appointed Chairman of the Department of Pediatrics. He is now Professor Emeritus at the University of California, San Francisco.

Early life

Abraham Morris Rudolph was one of five children born to Lithuanian Jews who had immigrated to South Africa. His father found work as a grocery clerk, sleeping on the counter when the store closed, finally becoming the owner of the store. His parents encouraged their children to pursue academic careers, and all three sons became pediatricians of stature in the international community (Figs 1 and 2).

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Figure 1.
The three Rudolph brothers circa 1930 at the Rudolph family home in Melville, Johannesburg. Jack is on the left, Natan is in the middle, and Abe is on the right.

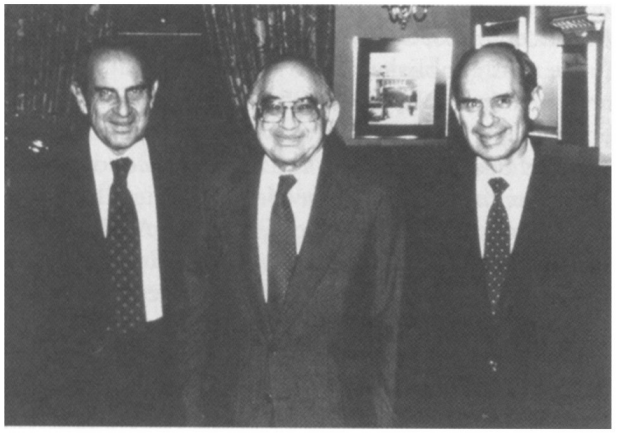

Figure 2.
The three Rudolph brothers in America. Abe is on the left, Jack center, and Natan on the right.

After graduating Summa cum Laude in 1946 from the University of the Witwatersrand Medical School, Abe, who was too young to practice as a physician, had to find work in a non-patient related area. He worked as an Instructor in Anatomy with Dr Joseph Lannon, a surgeon, and wrote his first paper on restrictive thoracic outlet syndrome.[1] While working in the anatomy laboratory, he met his future wife, Rhona Sax, who was a medical student at the time.

Dr Alexander Lee McGregor, an outstanding and thoughtful surgeon at the Johannesburg General Hospital, offered to sponsor Abe's studies abroad, should he wish to become a surgeon. Abe, however, decided to first gain some experience in pediatrics. He completed an Internship in Pediatric Medicine at the Transvaal Memorial Hospital for Children in Johannesburg, gaining substantial experience by working with talented pediatricians, such as Dr Sam Javett.[2] He then decided to continue in this field.

In February, 1949, Abe went to England for 9 months to study for Membership in the Royal Colleges of London and Edinburgh. He attended courses at the National Heart Hospital, and attended the clinic of Dr Richard Bonham Carter for Pediatric Cardiology at Great Ormond Street Children's Hospital. Because of his interest in neurology, he also attended clinics at the National Hospital for Neurology in Queen Square. After becoming a member, in 1949, of the Royal Colleges of Physicians of both London and Edinburgh, he went to Stockholm to work with Edgar Mannheimer at the Crown Princess Louisa Hospital. There he continued his studies in cardiology, and developed a special interest in pediatric cardiovascular physiology.

After this productive sojourn, Abe returned to South Africa, where he and Rhona were married. In 1951, he was awarded the degree of Doctor of Medicine by the University of the Witwatersrand. When his application for a position of registrar in pediatrics was not successful, the Rudolphs resolved to further their studies abroad, and Abe applied at three prestigious medical schools on the East Coast of the United States of America. It was Harvard, through the offices of Dr Charles Janeway, which was lucky enough to accept him.

Boston

The Harvard acceptance was for an unpaid position in Hematology or Neurology. Luckily for the future of Pediatric Cardiology, his visa application had been delayed, so he was unable to travel to the United States to assume this position. While pondering his options, he received a letter from Dr Janeway, offering him the chance to work in the Department of Pediatric Cardiology with Dr Alexander Nadas, recently arrived to head the new program. A benefactor had recently agreed to sponsor a position, with an annual stipend of $3000, so the decision to work in Pediatric Cardiology was easily made. He arrived in Boston at the end of August, 1951, knowing little about Dr Nadas, other than that he was extremely intelligent, an outstanding interpreter of electrocardiograms, and was also a foreign medical graduate. Together they would create and direct the course of Pediatric Cardiology in the United States.

In the initial period of the Fellowship, cardiac catheterization was not performed at the Children's Hospital. Angiography was performed using very primitive equipment. After injecting contrast medium into a peripheral vein, large X-ray cassettes were pushed manually in sequence in position under the patient, with a film exposed every 3 to 5 s. Dr Nadas

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referred the occasional patient to the Peter Bent Brigham Hospital to be catheterized by Dr Lewis Dexter and Dr James Dow. Only children above the age of 4 to 5 years were referred, and only the right heart was catheterized.

Several months after Abe started the fellowship, the fluoroscopy room in the Jimmy Fund Building became available intermittently to use for cardiac catheterization. Dr Walter Goodale, an adult cardiologist who had developed techniques for catheterization of the coronary sinus, was assigned to perform the studies in children. He instructed Abe in techniques of catheter manipulation, and the principles of hemodynamics.

After a period of fellowship, Abe wanted to further his studies in the physiology of the circulation. After discussion with Drs Nadas and Janeway, he began a fellowship in Physiology with Dr Clifford Barger at Harvard Medical School. Barger was interested in sodium metabolism in heart failure, and in the effect of digitalis on the excretion of sodium. To separate the general effects of digitalis from its direct effect on the kidney, Abe, with a colleague, Stan Rokaw, developed a method for chronic catheterization of the renal artery. This permitted injection of small amounts of digoxin into the renal artery specifically to study its effect on the excretion of sodium.[3] This technique provided the basis for chronic catheterization of the fetus using catheters made of polyvinyl chloride.

In 1955, Abe returned to the Children's Hospital in Boston as director of the cardiac catheterization laboratory (Fig. 3). Because of the high mortality of infants with congenital cardiac disease, he was anxious to try to make accurate diagnoses using catheterization. The catheters, however, were large, at 6 to 7 French-gauge, thick-walled, and extremely stiff. The bore was small, and the catheters clotted easily. There was great concern about perforating the heart. Dr Nadas thought that the risks were too high. The creation of 4 and 5 French catheters, and especially the Lehmann catheter, with its thinner wall and larger lumen making it easier to manipulate and less subject to clotting, made it feasible to consider doing catheterization studies in infants.

When Dr Nadas was on sabbatical leave in Groningen, Abe began catheterizing infants. After performing catheterization in infants, and appreciating the complexity of the lesions, he realized the importance of entering each chamber and great vessel in order to define each malformation. He promoted the use of the approach from the groin rather than the arm, which was then the usual approach. The information gained was vital for understanding the physiology of various congenital cardiac malformations. On his return to Boston, Dr Nadas was surprised but pleased with the results, and cardiac catheterization became established as a widely accepted procedure for diagnosis and delineation of hemodynamic disturbances in infants with congenital cardiac problems.[4,5] The ability to perform catheterization in infants made it possible for Abe to investigate the role of patency of the arterial duct in those with hyaline membrane disease. He and his group observed that all babies with hyaline membrane disease had widely patent arterial ducts.[6] It was not determined at that time, however whether the patency caused the disease, or was merely an association.

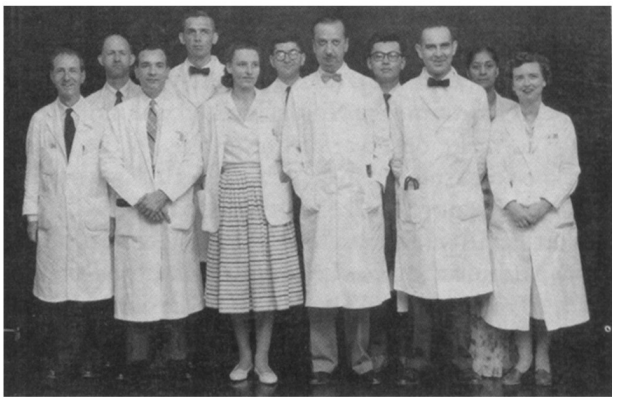

Figure 3.
This picture hangs in the old section of the Children's Hospital, in Boston Massachesetts. From Left to right: Paul Lurie, Julienne Hoffman, James Reynolds, Peter Auld, Laura Dewes-Tenchoff, Jerome Liebman, Alexandar Nadas, Art Sasahara, Abe Rudolph, an unknown cardiology fellow, and Jacqueline Noonan.

New York

In 1961, by convincing Abe and Rhona that New York was just as safe and civilized as Boston, Dr Henry Barnett, the Chairman of Pediatrics at the Albert Einstein College of Medicine, recruited him to become the Chief of Pediatric Cardiology.

It was there that Abe began his experimental work on sheep. His studies of hemodynamics in infants had led him to believe that the pulmonary circulation was extremely important in determining the course of congenital cardiac anomalies during fetal life, and particularly after birth. He therefore became interested in understanding the morphology and physiology of the pulmonary vasculature in the perinatal period. Dr Geoffrey Dawes had begun to publish information on the pulmonary circulation in fetal lambs, but these studies were performed acutely in fetuses that were removed from the uterus. In view of the extreme sensitivity of the pulmonary

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circulation to a variety of physiological changes, Abe wondered how representative these observations were of responses in undisturbed fetuses in their uterine environment. He decided it was important to try to make observations of fetuses in the womb under circumstances in which the fetus and mother were neither anesthetized nor stressed.

Fortuitously, at that time, Douglas Barron, well known for his studies in fetal lambs, was up the road, so to speak, at Yale. He and Giacomo Meschia had developed a method for placing catheters in the vessels of the ovine umbilical cord. They were interested in the techniques Abe had developed for chronic catheterization in the circulation in dogs and puppies. He introduced them to the use of polyvinyl catheters. In exchange, Abe learned the techniques of spinal anesthesia and the surgical approaches to the uterus in pregnant sheep. He decided that, rather than placing catheters in umbilical vessels, it would be more advantageous to place them in the arteries and veins of the limb, and developed techniques for chronic placement of catheters in the fetus. Subsequently, this led to the development of more sophisticated procedures in fetal surgery.

Michael Heymann joined Abe in 1963, and, together, they began to conduct experiments on the fetal circulation (Fig. 4). After they had perfected their chronic fetal lamb preparation, they had to address the issue of how to measure the flow of blood in the lungs. Because the fetal circulation is complex, methods such as dye dilution and the Fick principle, as used in adults, could not be applied to the fetus. The use of the Fick method combined with infusion of antipyrine had been used to measure umbilical blood flow, but it could not measure pulmonary flow or cardiac output in the fetus. In 1964, therefore, Abe began using an arduous technique based on radioactive microspheres, performing all calculations with very primitive equipment. After injecting the microspheres into the circulation, radioactivity in each organ was counted once, then the spectrometer was re-set in order to count radioactivity a second time. Microspheres were labeled with Cerium and Ytterbium, which had different spectrums of peak radiation, and thus could be discriminated. Abe recognized that the beauty of this technique was that it was possible to calculate relative flow of blood to every organ of the fetal body. Furthermore, if the flow of blood to any organ could be measured by some other method, it was possible to estimate the true flow within every organ and tissue. So, he and his colleagues used the antipyrine method to measure umbilical blood flow and thus, in conjunction with the microsphere method, were able to calculate the flows of blood to the organs. The measurement of flow of blood to the lungs, nonetheless, remained unresolved.

Abe struggled with this problem of defining the entire fetal circulation with this indicator method for a solid weekend. Then, on the Sunday night, the solution to the calculation of pulmonary flow came to him (Fig. 5).[7] Two simultaneous injections were required to make this calculation, one from the superior and the other from the inferior caval vein or the

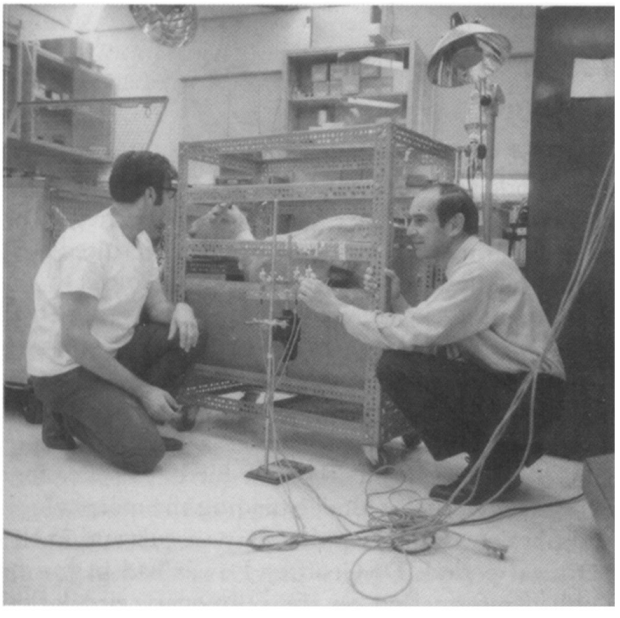

Figure 4
Abe Rudolph (right) and Michael Heymann (left) attending to one of their chronic instrumented fetal lamb preparations.

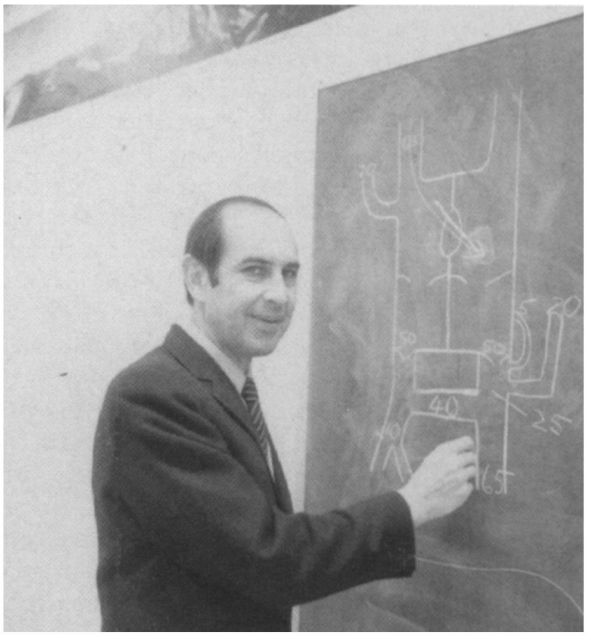

Figure 5
Abe at the chalk-board discussing aspects of the fetal circulation.

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umbilical vein. Abe believes that the introduction of techniques for chronic study of the fetus and the newborn, and the technique utilizing radioactive microspheres, are perhaps his most important contributions to the understanding of fetal circulatory physiology and the impact of perinatal circulatory changes in congenital cardiac disease.

His sojourn in New York was happy and productive. Besides the development of methods for studying the fetus in its natural environment, his team worked on the pulmonary circulation in calves, assessing the response of the pulmonary circulation to hypoxia and changes in acid-base balance. They produced the first paper showing the interrelationships between these variables and pulmonary vascular changes.[8]

Julien Hoffman, who had worked with Abe in Boston, joined the team in 1961. In Boston, they had studied pressure contours in patients with congenital heart block,[9] and in New York they collaborated on clinical research, including projects such as investigating the natural history of ventricular septal defects.[10]

California

Abe's reputation had grown, and in 1967, Dr Julius Comroe recruited him to the University of California, San Francisco. The offer was delivered on a hand-written sheet of Governor's House Hotel stationery, which was where Dr Comroe stayed when serving on various committees of the National Institutes of Health in Bethesda. Having just received approval for a large program project grant, he wanted Dr Rudolph to join him, because Dr William Tooley, who was to head the nursery, had recommended Rudolph as the ideal candidate. Dr Rudolph and Dr Tooley had met at a conference and exchanged ideas about the arterial duct.

Dr Rudolph moved to San Francisco accompanied by his colleagues, Drs Heymann and Hoffman, and there they began a large number of studies, using the fetal sheep model to investigate the physiology of the fetal circulation.

He was always interested in having the knowledge he gained from solving laboratory problems applied to patients, and vice versa. Nowhere was this more evident than in the body of work documenting the effect of prostaglandins on the arterial duct. A Swedish physician, Dr Thalme, had noticed that salicylates closed the arterial duct in rodents. Drs Rudolph and Heymann initiated a series of studies to investigate this effect in the fetal and neonatal lamb. After gaining experience with this pharmacological manipulation, they began to close the arterial duct in human infants, first using aspirin, and then Indomethacin, a more powerful inhibitor of prostaglandin synthetase. In tandem with Dr Friedman's group from San Diego, they published a paper on the use of Indomethacin in closing the duct in premature infants.[11]

As well as being engaged in the Indomethacin project, Dr Rudolph worked on the use of prostaglandin to keep the arterial duct open. Drs Cocciani and Olley had published their initial observations using isolated lamb ducts, showing that prostaglandin caused dilation, and Starling had reported that the duct could be opened in human infants by prostaglandin. Dr Rudolph's team began to pursue and extend these observations.[12]

Dr Rudolph's many observations in the lamb have enriched our understanding of the hemodynamics of the normal circulation in the fetus, the effects of stress on the circulation, and the effects of congenital cardiac lesions on prenatal circulation and circulatory development. In addition, they have helped us to understand the changes in the circulation that occur after birth, and the interrelationships between these changes and congenital cardiac anomalies. As one example, his work on ventricular hypertrophy following banding of the pulmonary trunk led to further studies of the mechanisms of myocardial growth before and after birth.[13]

He also contributed enormously to the field of obstetrics, where his investigations of circulatory physiology led to an appreciation of how different forms of stress such as hypoxemia, cord occlusion, and decreased umbilical flow, contributed to fetal distress. He also made seminal contributions to many areas of fetal physiology and biochemistry. He enjoyed collaborating with people from different disciplines, including collaborations in fetal endocrinology with Dr Peter Gluckman of New Zealand.[14] Also, he collaborated with Dr Les Benet to study pharmacokinetics and pharmacodynamics in the maternal-fetal unit.[15] Abe has looked upon his training of physicians who would go on to become world leaders in fetal and post-fetal research among his greatest contributions.

After 30 years as Chief of Pediatric Cardiology, Dr Rudolph assumed the position of Chairman of the Department of Pediatrics. He took on the role of educator seriously, devoting substantial energy to improving the residency training program. He also supervised a number of candidates for the degree of Doctor of Philosophy in physiology and pharmacology. Abe recalled particularly his supervision of Drs Laurene Wang and Harold Klopfenstein.[16]

The variety of committees, research boards, and councils on which he has served are too numerous to enumerate (Fig. 6). Of the prizes he has received, he feels honored particularly by receiving the prestigious Howland Award for Pediatrics, bestowed on him by

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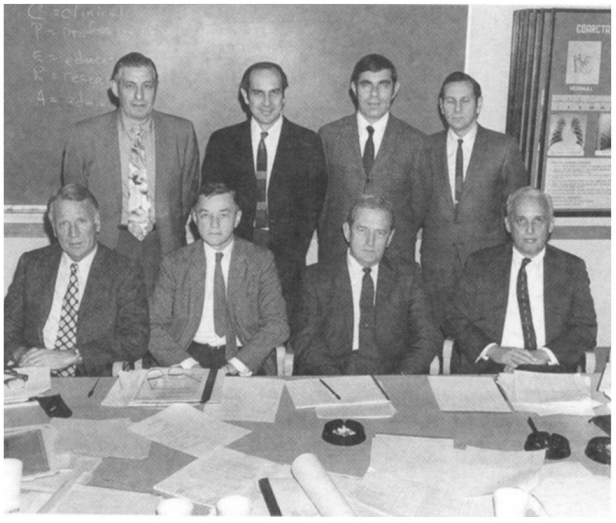

Figure 6.
Photograph taken at the conference to discuss the future of pediatric cardiology, held at the University California, Los Angeles, circa 1960. Front Row: Forrest Adams, Dan MacNamara, James DuShane. Sidney Blumenthal. Back Row: William Rashkind, Abe Rudolph, Norman Talner, Paul Lurie.

the American Pediatric Society in 1999, and the Research Achievement award, given by the American Heart Association in 1991, because it reflects the esteem of his peers.

The man

One of Abe Rudolph's refreshing attributes is that he always kept an open mind about research. His conferences with colleagues, fellows and students often sounded more like discussions, and he encouraged people to voice their opinions, listening to them with respect. He was never dogmatic, but was open to accepting different ways of approaching problems, and providing alternative solutions, an attitude that encouraged independent thinking in his students while giving him the opportunity to rethink his conclusions. He always had a special affection for his fellows, who have since populated Departments of Cardiology, Physiology, Endocrinology, Neonatology, Gynecology and Obstetrics around the world. His fellows have a special affection for him too.

Abe is a sought after internationally as a speaker, and has been invited to lecture all over the world. Of his many experiences, he regards his first trip to China in 1974, invited by the Chinese government, as one of the most memorable. The country had just begun a complete change in its direction, which he was privileged enough to experience first-hand (Fig. 7).

Throughout his career, Abe has been aided and supported by his wife Rhona, a physician of stature

Figure 7.
Abe Rudolph on his trip to China in 1974.

in her own right. Abe acknowledges that Rhona has had to sacrifice a great deal, including academic aspects of her own career. For example, she relinquished an academic position in the field of disability in Pediatrics when Abe came to San Francisco. Anyone who has met her has no doubt about her forceful character and intellect. Although her devotion was clear, she was never afraid to speak her mind to anyone, including Abe. She has also been intensely involved in the nurturing of their 3 children and their 4 grandchildren.

Abe and Rhona share many interests outside of medicine. Supporters of the Arts, they regularly attend the symphony, ballet and theatre. Both are ardent readers and adventurous travelers, and have seen much of the world. They have a home in Sonoma County, California, a stone's throw away from some of the finest California wineries, whose products they both enjoy (Fig. 8). In addition, Abe is a passionate gardener, his healthy annuals, perennials, and vegetable patch offering testimony to the same "golden touch" previously evident in his clinical and animal work.

Abe's work in the laboratory has been a model for all those who have ever worked with him, because he aspired to lead by example. He was the consummate research worker, conducting his own research, participating in experiments from incision to patch-placement to completion of physiological manipulations. He was able to modify experiments-in-progress, being familiar with all aspects of the work. He operated on all of his own preparations, and many of those of his fellows, and wrote his own papers, which were nearly perfect from the first draft. He rewrote those produced by his fellows, including those of one of the authors (Fig. 9). Within a day or two of their arriving on his desk, many of these papers were miraculously transformed and clarified after his editing. Last, but not least, he kept his work area

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Figure 8.
A current photograph of Abe and Rhona at their home, called "Kialami", in Sonoma, California.

Figure 9.
Abe Rudolph with of one of the authors, Norman Silverman, at the time of writing this article.

spotlessly clean, a remarkable feat for anyone who knows how messy sheep and fellows can be!

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