

LETTER TO THE NEWSLINE EDITOR

To the Newsline Editor:

I read with interest Dr. Henry Wagner's laudatory article "Hal Anger, Nuclear Medicine's Quiet Genius" (*J Nucl Med.* 2003;44[11]:26,28,34). I thought your readers might be interested in a few additional comments about Hal Anger and his work at the Donner Laboratory based on the 2 years I spent working with him.

I went to the Donner Laboratory in July 1962 to see if I could do research. Dr. John Lawrence, the director of the laboratory, hired me because he needed a radiologist to align the proton beam from the Berkeley cyclotron to treat the pituitary of patients with endocrine-responsive cancer, acromegaly, and diabetic retinopathy. I had just finished my radiology residency and was not sure whether I was going to be a diagnostic radiologist or a radiation oncologist. At the time, I had virtually no interest in nuclear medicine. My experience in nuclear medicine as a radiology resident at the University of Chicago (UC) earlier that year was comparatively rich for those days, but one of the reasons my enthusiasm had waned was exposure to Dr. Paul Harper's use of ^{99}Mo to scan the liver. He did this because a UC colleague (Dr. Leif Sorenson, a purine-pyrimidine metabolism expert) told him that molybdenum was a cofactor for xanthine oxidase, which was found in high concentration in the liver. Sorenson suggested that if Harper could find a molybdenum isotope, it would be a good agent for liver scanning. Harper, of course, found ^{99}Mo . He further figured out that he could use the $^{99\text{m}}\text{Tc}$ 140-keV isotope daughter to make the rectilinear scans. In fact, the technique worked, but the images generated were some of the worst rectilinear scans I had ever seen. (However, I have always believed that they served as a bridge for Harper to understand the significance of the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator that was subsequently explained to him by Brookhaven's Powell Richards during a plane ride back from an International Atomic Energy Agency meeting in Europe.) Looking at the liver scans generated using ^{99}Mo in 1962, my colleagues in residency and our faculty were of the general opinion this represented a waste of radiographic film.

With that background (which I, of course, did not tell Lawrence), I dutifully listened when he told me he had an engineer who had developed an interesting nuclear medicine imaging device and who really needed to collaborate with a physician. I said I would certainly like to find out about it, and he introduced me to Hal O. Anger. Hal gave me a few reprints about his camera, which he had recently finished. This was the first gamma camera most of you would recognize—an 11-inch version with 19 photomultiplier tubes. Before that, the only clinical work Hal had been involved in used his 4-inch camera with pinhole collimator to take pictures of the thyroid for Dr. Donald

Rosenthal, a physician on the Donner Laboratory clinical staff. These images were made because Lawrence was interested in treating thyroid disorders with ^{131}I . I read Hal's reprints and suddenly became quite curious. In particular, I was interested in the use of positron emitters. This camera had a coincidence system in place, with a tomographic readout using a simple backprojection analog technique. In his Newsline article, Wagner generously states that I immediately recognized the importance of Hal's camera; in reality, it is more appropriate to say that I was still feeling my way—but was clearly intrigued.

I need to point out that mine was a unique reaction. I subsequently found out that all the gurus in nuclear medicine at the time believed there was no future at all for the Anger camera. I remember that, at one SNM meeting I attended while still at Donner, Wagner predicted the future of nuclear medicine would rest with dual 5- or 8-inch rectilinear scanners. The late Dr. Joe Kriss (a wonderful nuclear pioneer from Stanford) had a chance to choose to buy either an early commercial gamma camera or a CO_2 breath analyzer and opted for the breath analyzer. Dr. George V. Taplin, a past SNM president and a beloved friend to virtually everyone who knew him (and on whom I bestowed the nuclear pioneer award—now the von Hevesy Award—when I was SNM president), once told me he thought the camera would never amount to anything. And when my future colleagues Harper and Bob Beck had published figure-of-merit calculations for the nuclear instrumentation of the day, the Anger camera came in last on the list. I hasten to add that Beck, rather sheepishly, later told me he did not include instrument sensitivity in his figure-of-merit calculations, but that when this parameter was added the Anger camera rocketed into first place by a wide margin.

When I joined Hal's group at Donner, my first assignment was to be sure that short-lived positron-emitting ^{68}Ga -ethylenediaminetetraacetic acid (EDTA) could be used safely in people. Using a series of distribution studies in rats, I was able to conclude that ^{68}Ga -EDTA had the same distribution as Ca-EDTA. Since I had used lots of Ca-EDTA in pediatric patients to treat lead poisoning when I was an intern in Chicago and since my studies indicated EDTA was the key biologic part of the tracer (with the ^{68}Ga essentially inert), I told Hal we could start scanning patients with suspected brain lesions using ^{68}Ga -EDTA and the positron version of the Anger camera (Fig. 1).

Wagner notes we were able to compare the results of our ^{68}Ga brain scans with those done with ^{203}Hg -neohydrin rectilinear scans that were generated by Dr. Ken McCormick at the University of California, San Francisco. It soon became clear to me that we had a winner.

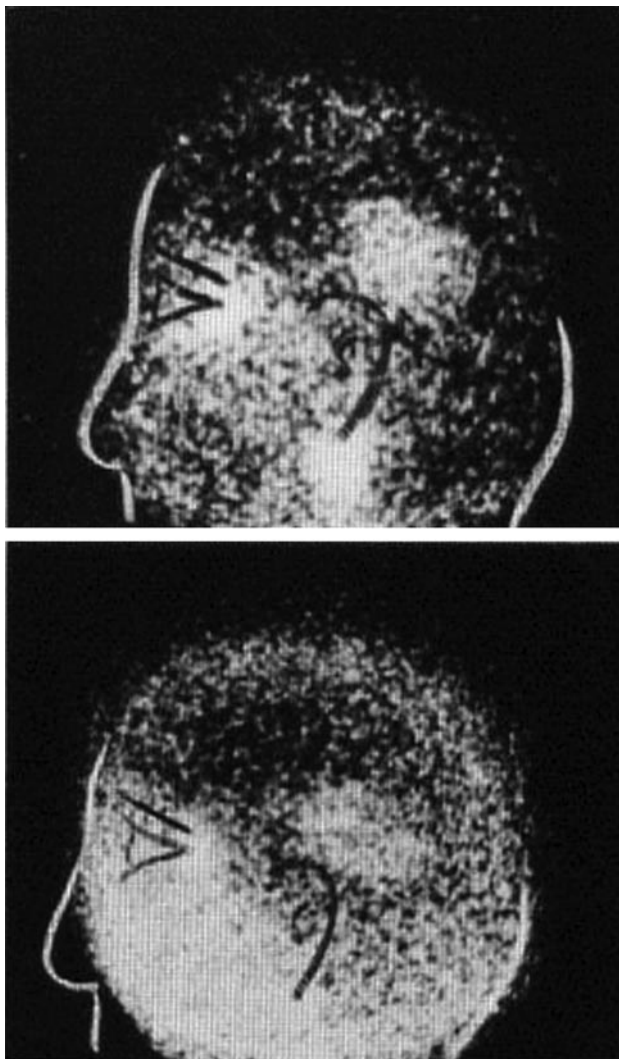


Figure 1. A ^{68}Ga -EDTA brain scan acquired with the Anger positron camera circa 1962, showing the tomographic capability. The brain tumor is in best focus in the top image, taken at about the level of the temporal horn. The bottom image is the next slice and is more peripheral. It shows more uptake in the soft tissues of the calvarium and less in the tumor.

We were able to generate better pictures faster, covering more of the brain in much less time.

Wagner also notes that we were able to move Hal's 11-inch camera with multichannel collimator to the Alta Bates Hospital in Berkeley. We did this for 2 reasons. The first was to be sure this camera could be used extensively without Hal next door to tinker with anything that might be amiss. The second was to expand our abilities to image a variety of patients. We wished to test the camera in a more conventional mode, using then current diagnostic tracers and doses and the camera with a multichannel parallel-hole collimator. Wagner noted that the earliest pinhole camera needed therapeutic ^{131}I doses to make an image, but we had no trouble imaging the thyroid with standard diagnostic ^{131}I doses. However, the camera at the Alta Bates Hospital had a nonrotating fixed head. This

prompted Hal to create a triple pinhole collimator for thyroid imaging to obtain precise anterior oblique thyroid images (Fig. 2). We used ^{203}Hg -neohydrin and ^{131}I -hippuran for the kidneys and ^{131}I -rose bengal for the liver (Figs. 3–5). I remember hearing Professor M. Ter-Pogossian say at a Radiological Society of North America refresher course that the Anger camera would never be as good as rectilinear scanners because its best resolution was at the surface, whereas the rectilinear scanners had better resolution at depth. My personal reaction was that although the physics behind this statement might be true, the ability of the gamma camera to image rapidly any organ in multiple projections more than made up for this resolution difference.

This was illustrated to me by experience with a patient at Alta Bates who was dying from a fever of unknown origin. The physician caring for her (Dr. M. Myers, an excellent internist in Berkeley) asked us to do a ^{131}I -rose bengal liver scan, because that was about the only test that he could think of that had not yet been done. None of the other tests offered a diagnosis. The patient did not have significant liver tenderness, but Myers thought perhaps her liver had become slightly larger since her initial hospital exam. The Anger camera at Alta Bates had a stationary detector, and only the patient bed could be

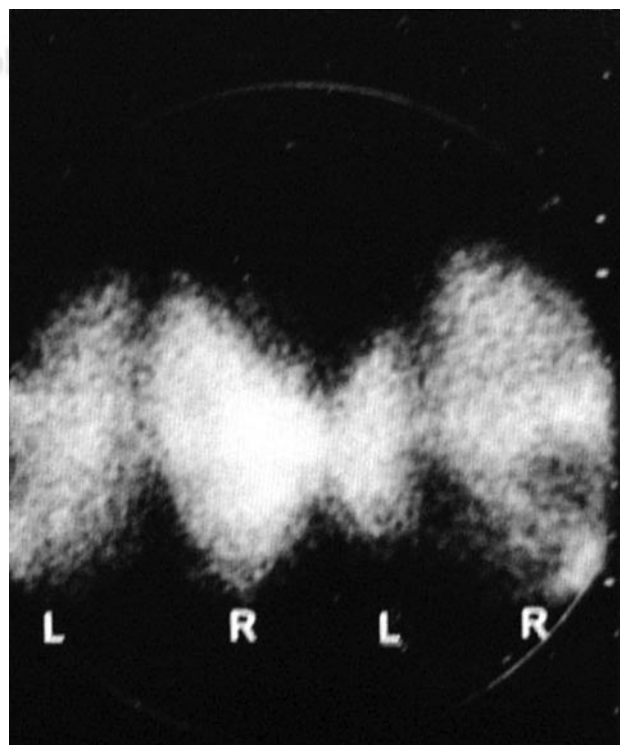


Figure 2. Hal Anger designed a triple-pinhole collimator for use with ^{131}I in the thyroid. With this collimator, anterior and both anterior oblique views could be obtained at the same time. Note how much better the cold nodule in the right lobe is seen by the oblique pinhole compared with the straight anterior pinhole. Also note the side inversion present on the Polaroid readout with the oblique pinholes.

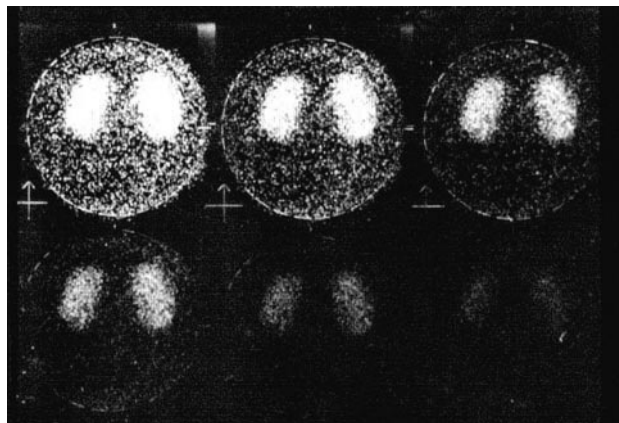


Figure 3. In the early 1960s, there were no computers to store and replay images until the correct exposures were obtained. This could have been a real problem, even with the relatively short camera imaging times (compared with then current rectilinear scanners). Hal Anger solved this by taking multiple images of the Anger camera readout cathode ray tube with a single Polaroid exposure, outfitting the Polaroid camera with multiple lenses set about one-half F-stop apart. The figure shows this technique and normal kidneys using ^{203}Hg -neohydrin. Middle images have optimal exposure.

moved up and down. There was not enough space to permit a lateral view, but we could get an anterior and posterior projection—clearly better than the standard rectilinear scan of the day, which was done only in the anterior projection. The patient’s anterior view was entirely normal, but I noted a mass in the dome of the liver on the posterior image. Given the history, I diagnosed a liver abscess. Her doctors believed that the lady would either survive or die on the operating table, depending on what was discovered, but that she would certainly die if nothing was done. So she went to the operating room, where the liver was found to appear entirely normal. It is my understanding that my lineage was called into serious question at this time. Nevertheless, because of the rose bengal study, the surgeon elected to needle the posterior aspect of the dome and was both surprised and gratified when an extensive amount of pus came gushing out. The patient survived a rocky postoperative course and ultimately did well. The case gained much favorable notoriety at Alta Bates. A few weeks later, when I allowed Hal to come and see his machine (which, incidentally, did very well without him), we ran into Myers, who said to Hal, “This lady is alive for 3 reasons. First, I ordered the test; second, Gottschalk diagnosed the abscess; but, third, and most important, you invented the machine.” I then escorted Hal to the doctors’ lounge. When I introduced him to the physicians who had come in for their morning coffee, they all stood up and applauded.

Wagner notes that John Kuranz, then president of Nuclear Chicago, had the foresight to begin the commercial development of Hal’s camera. Toward this end, in the fall of 1963, Kuranz sent Phil Shevick, an engineer at Nuclear Chicago, to talk to Hal to plan the development

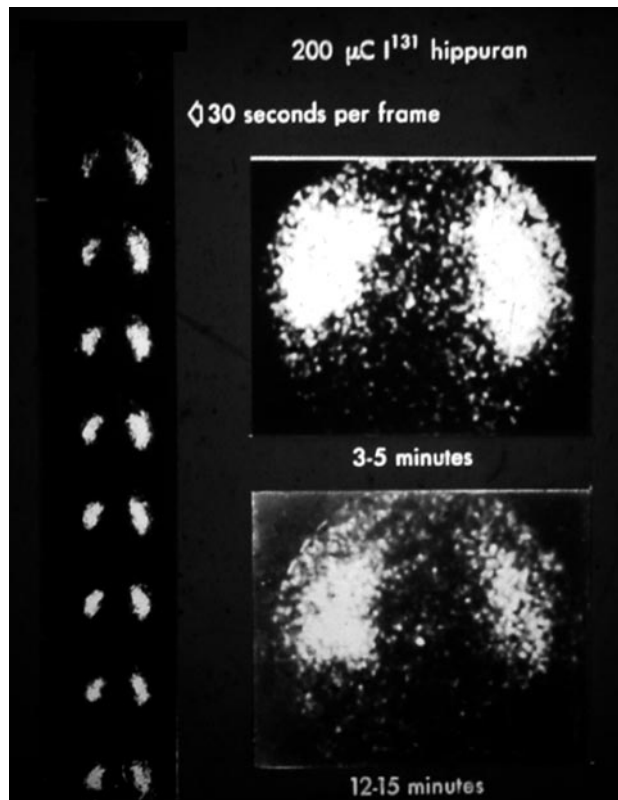


Figure 4. First dynamic camera renal study. The patient had left renal artery stenosis. The slow left perfusion, the small left kidney, and the delayed left-sided excretion seen at 12–15 minutes are characteristic. Although this image was made from an old color slide, these findings can be seen.

of Nuclear Chicago’s scintillation camera. Shevick was clearly excited and talked to me about building an even better camera than Hal’s. He was going to use transistors, whereas Hal had built his camera with vacuum tubes—the old-fashioned way. It is interesting that it took Nuclear Chicago several years to make a camera as good as the initial camera that Hal built with his old-fashioned vacuum tubes. Along with Shevick came Edward Reibel, the

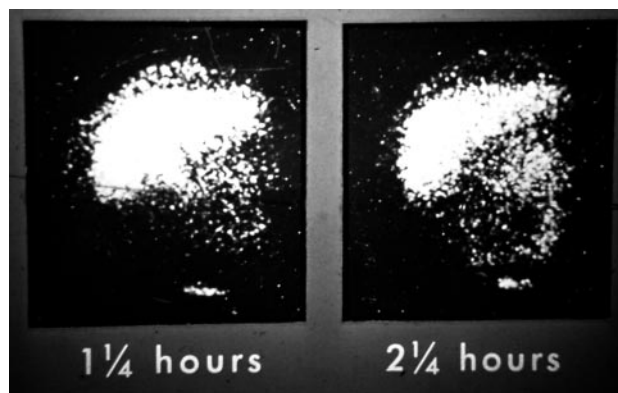


Figure 5. This infant had extrahepatic biliary atresia that had been repaired. At the time of this study, the baby had symptoms of biliary obstruction. This ^{131}I -rose bengal scan shows gut activity at 2.25 hours, indicating the repair is still patent.

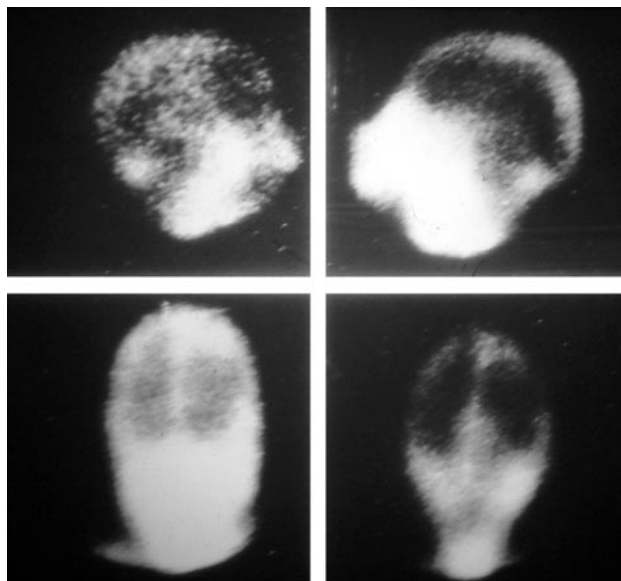


Figure 6. ^{99m}Tc -pertechnetate brain scan. This was the second or third such study we made. We were amazed at the count rates obtained, and so we tried the first cerebral brain angiogram using a lateral view (upper left). This was such a new concept that I had not yet figured out that the anterior view would be better.

sales manager for Nuclear Chicago. While Shevick and Anger discussed how to make the camera, Reibel and I talked about the commercial possibilities. Reibel was very concerned and was quite dubious about the future of the gamma camera. He said the first gamma camera would sell for about \$25,000, which was twice the going rate for the current commercial 3-inch rectilinear scanner, and he wasn't sure that anybody would buy it. The next time I saw Reibel he and Nuclear Chicago had parted ways.

In the spring of 1964, we had a visit from Dr. Richard Peterson, who was the Director of Nuclear Medicine at the Veterans Administration Hospital in Iowa City, IA. Peterson had been to Chicago, where he persuaded Harper to do a brain scan on him with his new wonder tracer ^{99m}Tc -pertechnetate. Harper is a superb thyroid surgeon and was initially interested in pertechnetate as a thyroid tracer. However, he had stopped by the exhibit that Hal and I had at the SNM meeting in 1963, where we showed brain scans done with ^{68}Ga -EDTA. In that exhibit, I described ^{68}Ga -EDTA as a nonspecific extracellular space tag. Harper found me, and we sat down for the first of many serious conversations that I would have with him. (He subsequently became my colleague and mentor in the decade I spent at UC.) At that time, he wanted to know why I described ^{68}Ga -EDTA the way I did. When we finished our discussion, he told me that he had a new extracellular space tracer called ^{99m}Tc -pertechnetate, and he thought he had better go and try it for brain scans. For about the next 10 years, until CT brain scans became established, pertechnetate brain scans were the mainstay of most nuclear medicine departments. Doing 8 or 10 brain scans a day was common practice in the larger facilities.

Having received his brain scan at UC as a volunteer, Peterson went back to Iowa, traveling by train for more than 18 hours. He had a prototype commercial gamma camera, one of the first 2 ever made with an 11-inch crystal. He said that even after the long trip, he still had enough counts in his head to get a decent image in a reasonable amount of time. Apparently, because he was not at an Atomic Energy Commission facility like Brookhaven or the Donner Laboratory, it was not possible for him to get a technetium generator, so he suggested that we get one. Hal and I thought this was a very good suggestion, so Hal ordered a technetium generator from Richards at Brookhaven. Three weeks passed, and we could not understand what had happened to our technetium generator. Hal made inquiries, and we found that someone in the mailroom had received the package from Brookhaven and noted that it was clearly labeled as an isotope generator. This individual knew what he should do with generators, and he promptly took it to the electronics shop up above the Donner Laboratory, halfway up the hill at the Lawrence Radiation Laboratory—because that's where all electric generators went. The shop kept it for Hal for the 3 weeks in question, assuming he would pick it up when he needed it. Wagner notes that Hal is a quiet man. I believe that is true 99% of the time. Hal's interaction with the mailroom attendant responsible was representative of the other 1%. We reordered the generator, which the attendant hand delivered to Hal's office the moment it entered the Berkeley campus.

In the spring of 1964, we performed our first gamma camera multiview ^{99m}Tc -pertechnetate brain scans, the
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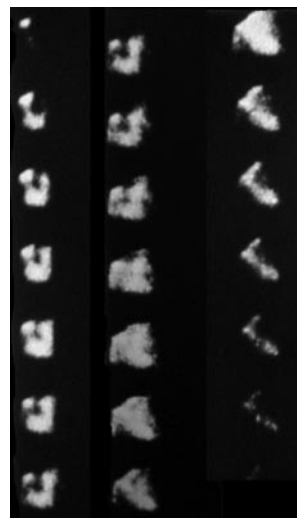


Figure 7. The first dynamic heart study performed with an Anger camera. One-second images were made after an intravenous injection of 10 mCi ^{99m}Tc -pertechnetate. Images from author's personal collection. Originally published in *Seminars in Nuclear Medicine*.



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whereas ^{99m}Tc -tetrofosmin is used less frequently. Thallium is still the choice for viability purposes only.

The main clinical indications for nuclear cardiology studies are prognosis and risk stratification, followed closely by diagnosis and therapy evaluation. The demand for functional testing of myocardial viability is relatively low. With a few exceptions (such as in Argentina), nuclear cardiology studies are usually interpreted and reported by nuclear medicine physicians. Postgraduate degrees in cardiology are available in most countries and in nuclear medicine in a few, but to date no degree in nuclear cardiology is available. The Ibero-American Society of Nuclear Cardiology was founded in 1994 in Pucon, Chile, with members from Latin America, Spain, and Portugal. Since then, a symposium has been held every other year with participation from nuclear physicians, cardiologists, technologists, and scientists and both regional and extraregional lecturers and experts.

Some challenges to nuclear cardiology continue to make growth difficult in some areas of Latin America,

including: the high cost of radiopharmaceuticals; few continuing education opportunities; lack of cardiology background by reporting nuclear medicine physicians, as well as lack of nuclear medicine background by reporting cardiologists; and the fact that many potential referring physicians and health managers are not fully aware of the clinical benefits and cost effectiveness of nuclear testing. Local production of radiopharmaceuticals and other supplies should be encouraged, cross-educational programs in cardiology and nuclear medicine should be organized and implemented, and education of physicians and managers should be accomplished through evidence-based approaches. Other strategies include: the establishment of accreditation and recertification procedures, the inclusion of pre- and post-degree education in nuclear cardiology, the organization of nuclear cardiology activities within cardiology meetings, and public information about the benefits of noninvasive testing.

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first complete camera brain scans performed after Peterson's rudimentary one (Fig. 6). We expected a good count rate compared with some of the other tracers we had used but were astounded to see how many more counts we got from ^{99m}Tc than we did from the positron brain scans we were used to. In those days, a standard single-view scan with a 3-inch rectilinear scanner (the workhorse of nuclear medicine at the time) could take as much as 45 minutes. We could do a positron scan with ^{68}Ga -EDTA in about 12 minutes. We got more counts in 2 minutes with ^{99m}Tc -pertechnetate than we ever got with ^{68}Ga -EDTA. Later that spring, we took the first camera dynamic cardiac images using ^{99m}Tc -pertechnetate (Fig. 7).

Wagner gives me credit for helping Hal modify his camera to develop his longitudinal whole-body scanner using a scanning gamma camera with a focused collimator. Much as I wish it were true, I had left the Donner Laboratory to work at UC when Hal fully developed his tomographic rectilinear scanner. I was fortunate enough to publish one of the first accounts of this device and to have one of the earliest commercial versions, which we used primarily for gallium studies when I was at Yale. The tomographic scanner was not a commercial success. However, I have believed for some time that new technetium-labeled receptor tracers are likely to be developed which could benefit from a whole-

body imaging device with variable resolution at any depth required (e.g., around the periaortic area). Using today's large crystal cameras with available fanbeam collimators would make it possible to develop computer software programs that would recreate Anger's tomographic scanner with relatively little effort. We may well see this device flourish in the years to come.

If you gather from all this that I am lucky to have been in nuclear medicine at all, I believe you are correct. Luck and curiosity on my part started my relationship with Hal Anger. But Hal's personality had as much to do with it as anything. Wagner has called him quiet and unassuming. I worked in Hal's lab, and he was the boss—although he was never bossy. When we disagreed, common sense and science were always used to resolve differences. I was attracted to nuclear medicine not only by Hal's camera, which took better pictures than I was used to seeing, but by Hal's personality, which made it very easy to work with him. For more than 40 years, Hal has been a good friend. Wagner notes that nuclear medicine has been profoundly affected by Hal Anger. We are very fortunate to have had him in our field.

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