infants with influenza-associated croup, and in individuals whose community function requires that they be returned to work as soon as possible. Other groups may also be suggested for both therapy and prophylaxis once there is a better understanding of the pharmacokinetics of the drug and its efficacy in infants and children.

Although not strictly within the scope of their charge, the panel also made some other recommendations. They argued especially that there is a need for new procedures and facilities to enable rapid diagnosis of influenza A infection. This would ensure that the drug is used only to treat viral infections against which it is effective. The panel also encouraged the study of analogs of amantadine, especially rimantadine, that appear to have greater efficacy and fewer side effects.

Apparently anticipating the panel's recommendation, Du Pont increased its stockpile of Symmetrel to nearly four times its normal size. The company now has enough amantadine on hand to treat 5 million individuals for 10 days, a stockpile with a retail value of about $25 million. That is enough to handle regional outbreaks of influenza A, but not enough to handle an epidemic or a pandemic. Production of the drug takes about 6 months, and therefore it would be in short supply if stockpiles are depleted by an epidemic. Because of the poor reception of the drug by physicians in the past, however, the company probably does not feel justified in increasing the stockpile. Only time will tell, therefore, whether the drug will make a significant contribution the next time the influenza virus undergoes an antigenic shift and once more starts its travels around the world.—THOMAS H. MAUGH II

The 1979 Nobel Prize in Physiology or Medicine

The 1979 Nobel Prize in Physiology or Medicine has been awarded to Allan MacLeod Cormack, 55, of the Physics Department, Tufts University, Medford, Massachusetts, and Godfrey Newbold Hounsfield, 60, of the Central Research Laboratories of EMI, Ltd., Hayes, England, for the invention of the x-ray diagnostic technique computer-assisted tomography (CAT), also known as computed tomography (CT).

At a recent international meeting, a distinguished British radiologist opened the proceedings with a paper dedicated to the history of CAT. After his presentation, a member of the audience commented on the pioneering work of Cormack. The speaker, quite candidly, stated that he was not aware of Cormack's contribution. This widespread lack of awareness, even among the cognoscenti, of the work of one of the 1979 Nobel laureates, is one of several unusual, indeed unprecedented, features of this year's award. Other unusual features are the fact that the two honored investigators have no background in biology or medicine and that their discovery is not in the "basic" life sciences but rather in "applied" research. The history of the development of CAT—an extraordinary technique which in little more than 7 years after its introduction has had an unmatched impact on the radiological sciences (*1*)—is fascinating and in many respects instructive.

Cormack, born in South Africa and educated at Cambridge University in nuclear physics, was a member of the physics faculty at the University of Capetown when, in 1956, the affiliated Groote Shuur Hospital lost their regular physicist and called the Physics Department for help. Because Cormack was the only nuclear physicist available, he was assigned to the hospital for $1\frac{1}{2}$ days per week, during which time he supervised isotope administration and film badge calibration and performed other duties of a radiological physicist. His involvement with radiotherapy treatment planning demonstrated to him the need for accurate values of attenuation—that is, the amount the x-ray beam weakens as it passes through the patient's anatomy—and led him to wonder if these could be obtained from x-ray measurements made outside the body. It occurred to Cormack that if enough x-ray projections or views were taken at a variety of different angles, there would be enough information to determine uniquely and quantitatively the internal structure and, further, that images reconstructed in this manner could be diagnostically useful. That fall he went on sabbatical to the Cambridge Electron Accelerator at Harvard University, where he took enough time from his regular research to derive a mathematical theory for image reconstruction. Upon his return to South Africa in 1957, he proceeded to test the theory with a laboratory simulation. The test object was a circularly symmetrical assembly of aluminum and wood; because it was symmetrical, only one projection was needed. Projection data were taken using a collimated beam from a 7-mCi ^{60}Co source, which emits gamma rays with energies of 1.2 and 1.3 MeV, and using a Geiger counter as the radiation detector, while the object was translated through the beam in 5-mm steps. The data were then mathematically processed to obtain the attenuation coefficient as a function of radius; the results agreed nicely with the known construction of the phantom.

Late in 1957, Cormack moved to the United States to join the Physics Department of Tufts University. While doing other research, he continued to putter with his pet project until he derived an alternative mathematical approach that was better suited for calculation. In 1963 he repeated the experiment with similar equipment, but with a nonsymmetrical phantom of plastic and aluminum. This time the data processing was too extensive for hand calculation and computers were used. Cormack showed his results to several radiological physicists, but was unable to uncover any interest in his idea. The two experiments were published in the *Journal of Applied Physics* (*2, 3*), with the hope that they would be noticed. They were not.

Hounsfield's early and totally independent work began 10 years after Cormack's. His inspiration came not from a medical environment, but from pattern recognition studies at the Central Research Laboratories of EMI. In 1967 he speculated that mathematical techniques might be used to reconstruct the internal structure of a body from a number of x-ray transmission measurements. Like Cormack, he realized that a tomographic approach was the most practical; any three-dimensional body could be divided into slices and each slice could be examined by, and reconstructed from, radiation passing only through it. This approach reduces the three-dimensional problem to a two-dimensional one. Before performing his first experiments, Hounsfield calculated the theoretical accuracy of the technique and concluded that with normal dose levels it would be possible to measure the absolute value of the x-ray attenuation coefficient with an accuracy of 0.5 percent—almost 100 times better than that of conventional methods. This realization was of great importance, because the success of CAT is due to the fact that not only can internal structure be displayed, but very small density differences can be distinguished, so that in head scanning, for example, cerebral fluid-filled cavities and even differences between gray and white matter can be recognized.

Hounsfield's first apparatus was similar to Cormack's except that an americium source and a crystal detector were used. His method of image reconstruction was easier to implement than that employed by Cormack, and he proceeded immediately with nonsymmetrical test objects. The results were so encouraging that an x-ray tube was substituted for the radionuclide source so that data gathering could proceed faster—9 hours instead of 9 days! At this time Hounsfield was able to generate interest at the British Department of Health and Social Security and on the part of two farsighted radiologists, James Ambrose and Louis Kreel. With their help, he scanned sections of preserved human brain, fresh bullock brains, and numerous carcasses of pigs.

The first clinical machine for head scanning was installed at the Atkinson Morley's Hospital, Wimbledon, in 1971. The scanning motion consisted of a synchronous translation of source and detector, alternating with 1° angular rotations, until 180 projections were measured. It required $4^1/_2$ minutes to gather data, followed by an additional 20 minutes for image reconstruction, which was reduced to several minutes when a newer minicomputer was incorporated into the system. After a period of $1^1/_2$ years for the collection of clinical data, a presentation was made at the April 1972 annual meeting of the British Institute of Radiology, followed by publication in 1973 (*4*).

It has been reported that EMI initially estimated that the worldwide market would be less than 25 scanners. In fact, there are now over a dozen manufacturers (at one time over 20), the total number of scanners presently installed is well over 2000, and hundreds of new scanners are being manufactured each year. Many improvements have been made: the water bag, which Hounsfield had used to equalize the x-ray attenuation and thereby reduce artifacts, has been eliminated, and most current machines have apertures large enough to do body scanning as well as heads (*5*). The number of detectors has increased to as many as 1088, and with most new machines only one gantry motion is used (rotation) because the detector array can measure simultaneously a complete set of ray sums through the body (fan-beam scanning). Finally, data processing has been reduced to a few seconds by using sophisticated special-purpose computer circuitry, even though the size of the image matrix has increased from 80 × 80 picture elements to as many as 512 × 512, with a concomitant improvement in resolution from 3 mm to as low as 0.375 mm. In fact, the general level of design and performance of present-day scanners bears the same relation to the EMI Mark I scanner, the first commercial unit, as this device bore to Hounsfield's laboratory apparatus.

Along with these improvements has come a cost escalation, from about \$300,000 for the EMI Mark I to prices exceeding \$800,000. The high cost and the sudden intense demand for CAT scanners have brought them very much into the public eye, and they have become either a scapegoat for, or a prime example of, the high cost of medical care, depending on one's point of view. In any event, these machines are able to produce strikingly clear, uncluttered images of internal body structures. This success is a product of three factors: the mathematical approach to tomographic reconstruction (*6*), efficient electronic detection, and the use of highly collimated beams, which markedly reduce the fogging effect of scattered radiation.

The fundamental problem which confronted Cormack and Hounsfield was that of obtaining accurate measurements of the x-ray attenuation coefficient at all points within the section being examined. The attenuation coefficient is defined as the relative intensity loss per centimeter for a collimated x-ray beam traversing the object. Bone, for example, is highly attenuating, while most soft tissues have coefficients slightly higher than that of water. The difficulty is that,

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Godfrey N. Hounsfield

without cutting the body into small pieces for individual measurement, one is limited to measurements of total attenuation along the ray path lying between the x-ray tube and the detector. This total attenuation or ray sum is essentially a line integral of the attenuation coefficient along the specified ray. Mathematically, if $f(x,y)$ represents the attenuation coefficient as a function of position in the imaging plane, and $p(r,\phi)$ is the path integral along a ray at angle ϕ to the y axis and at a distance r from the origin, we can write

$$p(r,\phi) = \int_{r,\phi} f(x,y)\, ds \qquad (1)$$

where s is path length and the line integral is taken along the ray specified by r and ϕ. The problem is simply to invert Eq. 1—that is, given values of p, find the f values in the plane that are consistent with them.

Cormack's approach was to expand both p and f in a Fourier series in the azimuthal angle, thereby obtaining a one-dimensional integral equation in the radial coordinate, the solution to which involved integrals of functions of Tschebycheff polynomials. For circular symmetry only one term in the Fourier series was required, and the integral could be done easily. In Cormack's second paper (*3*) devoted to the nonsymmetrical example, he expanded the radial functions in an orthogonal set of Laguerre and Hermite polynominals, which made the calculations more manageable.

Hounsfield's approach was mathematically less elegant but more intuitive. (Hounsfield has been quoted as saying, "I find I've got other tools of thinking than math.") Recognizing that data and image values could be obtained only at finite intervals, he divided the tomographic slice into elements (for example, 3 × 3 × 13 mm) and replaced the continuous equation (Eq. 1) by the discrete equation

$$p_j = \sum_i w_{ij} f_i \qquad (2)$$

where w_{ij} is the weighting factor that gives the contribution of the ith element to the jth ray sum, and the sum is taken over all elements. Hounsfield solved this equation for f_i using an iterative, or trial-and-error, approach. That is, he started with an arbitrary set of f_i (for example, a constant) and continually adjusted their values so that the calculated ray sums would agree with the measured ray sums as they were examined in a prescribed sequence. This process was repeated until a sufficiently accurate reconstruction was produced.

It is a curious fact that the mathematical procedure used in present-day scanners is neither that of Cormack nor Hounsfield's original technique, but, surprisingly, dates back to 1917. Cormack had stated in his 1963 paper: "One would think that this problem would be a standard part of the 19th century mathematical repertoire," but as he later discovered and reported, the problem of determining a function from its line integrals was first solved by Johann Radon in 1917. This Austrian mathematician had actually obtained a direct inversion of Eq. 1, which eluded both Cormack and Hounsfield. Radon's solution can be written

$$f(x,y) = \frac{1}{2\pi^2} \int_0^{\pi} \int_{-\infty}^{\infty} \frac{\partial p(r',\phi)/\partial r'}{r - r'} dr' d\phi \qquad (3)$$

where $r = x \cos \phi + y \sin \phi$ is the radial coordinate of a ray passing through (x,y) at angle ϕ. Interestingly enough, Radon's derivation was concerned with the solution of gravitational field equations and had nothing to do with image reconstruction. The inner integral in Eq. 3 can be thought of as a mathematical filtering of each projection (that is, of all ray sums at a single angle ϕ). In present scanners the filter operation generally is based on a different but mathematically equivalent integral. The outer integral then represents a superposition or average over angle of all filtered rays which intersect the point (x,y). This method is called filtered back-projection, because the superposition process (that is, the ϕ integral) is equivalent to a back-projection of the filtered ray sums onto the image plane. It is of some interest that Hounsfield later replaced his iterative approach with a procedure similar to Radon's solution, except that the filtering coefficients were obtained from an iterative solution for point sources rather than from an analytic expression.

The story is not complete without mentioning that the solution to the image reconstruction problem has reappeared throughout the late 1950's and 1960's in a number of areas and to a number of people. First was Ronald N. Bracewell (*7*), who developed both an analytic method equivalent to Radon's and an iterative method for reconstructing images of the sun from microwave data taken with "strip" antennas. These and other methods were developed independently in fields as diverse as radiography, optics, and the study of biomolecular structure by electron microscopy.

In the radiological area, where the benefits have led to the Nobel award, two scientists must be singled out. One is William H. Oldendorf, an American neurologist who, deeply frustrated by the gross inadequacy of x-ray images, particularly skull roentgenograms, had for many years valiantly fought against the calvarium, this forbidding barrier to the underlying brain. In 1969, Oldendorf devised, implemented, and patented an apparatus similar to Cormack's, but using a simple electronic RC (resistance-capacitance) circuit for "reconstructing" internal points, instead of a calculator or computer (*8*). The other scientist, David E. Kuhl, an American nuclear specialist working primarily with radioisotope imaging and secondarily with transmission images used for orientation purposes, also developed an electronic method of image reconstruction (*9*). Kuhl, incidentally, is the undisputed originator of emission (radionuclide) CT, a technique which, coupled with neurochemical and radiochemical advances, offers recent promise of providing physiologic and metabolic information, similar to what transmission (x-ray) CT has produced in such striking fashion in the anatomic and pathologic areas. While these two investigators, whose work was done in the same time period as Cormack's, must be credited with great intuition and ingenuity, the reconstruction problem required a mathematical solution. [Kuhl later (1973) developed an iterative mathematical procedure for use with the isotope imaging.] In fact, the methods suggested by these two American scientists, although conceived through different intuitive approaches, correspond to the same mathematical approximation. This approximation is now called simple back-projection and is indicated by Eq. 3 with the inner r' integral replaced simply by $2\pi^2 p(r,\phi)$. Thus it represents a back-projection of the ray sums without any prior filtering. The images so obtained are significantly blurred, and could never have produced the diagnostic breakthrough that CAT did.

The obvious question, with so many independent discoveries, is why it remained for Hounsfield to achieve true tomography, a goal pursued for so many years by means of focal plane and related radiographic film techniques (Bocage, Vallebona, Ziedses des Plantes, Grossmann, who coined the word tomograph, Takahashi). Among many determining factors, the following three need to be mentioned: first is the mathematical solution to the image reconstruction problem; second is the recognition of the diagnostic need; third is the engineering technology to produce a successful clinical machine. Only Hounsfield was able and had the opportunity to achieve this synthesis. With their choice, the Nobel Prize Committee and the Nobel Assembly have recognized, apparently after some debate, that the frontiers of science cannot be compartmentalized and parochially limited to selected areas. Regardless of whether the contributions are in basic or applied scientific fields, originality and benefit to ailing mankind are the critical ingredients. These two hallmarks characterize this year's choice for the Nobel Prize in Physiology or Medicine.

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References

1. G. Di Chiro, *Am. J. Roentgenol.* **122**, 659 (1974).
2. A. M. Cormack, *J. Appl. Phys.* **34**, 2722 (1963).
3. _____, *ibid.* **35**, 2908 (1964).
4. G. N. Hounsfield, *Br. J. Radiol.* **46**, 1016 (1973).
5. R. S. Ledley *et al.*, *Science* **186**, 207 (1974). L. Twigg, *Science* **186**, 207 (1974).
6. R. A. Brooks and G. Di Chiro, *Phys. Med. Biol.* **21**, 689 (1976).
7. R. N. Bracewell, *Aust. J. Phys.* **9**, 198 (1956).
8. W. H. Oldendorf, *IRE Trans. Bio-Med. Electron.* **BME-8**, 68 (1961).
9. D. E. Kuhl and R. Q. Edwards, *Radiology* **80**, 653 (1963).