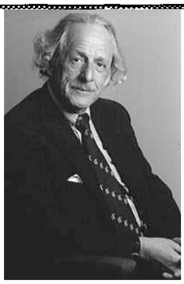
Essays of an Information Scientist: Science Literacy, Policy, Evaluation, and other Essays, Vol:11, p.335,1988 Current Contents, #42, p.3-11, October 17, 1988



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# Noninvasive Medicine. Part 2. Newer Diagnostic Technologies

Number 42 October 17, 1988

**This essay (the second of three parts) continues our examination of painless medicine. First, the concept of "noninvasive medicine" will be defined. The essay will then present a sampling of noninvasive diagnostic technologies. These include current imaging techniques, such as computed tomography, ultrasound, and magnetic resonance imaging. Examples of nonimaging diagnostic methods are also presented. Research-front data will further identify important developments in the area of diagnostic medicine.**

In Part 1 we discussed the pain and anxiety often associated with medical treatment.[1] We began our discussion of painless medicine with the most obvious and universal source of pain and anxiety for patients, young and old—needles. We also looked at some of the less invasive alternatives to needles—pumps, pills, or patches for administering medication; and neurostimulation, acupuncture, or hypnosis for managing acute pain.

Painless medicine is realized through a host of less intrusive and less painful technologies. These fall into two distinct groups—diagnostic and therapeutic—and will be reviewed in Parts 2 and 3.

Part 2 first defines noninvasive medicine, then maps some current medical technologies on a scale of noninvasiveness. It also presents a sampling of current diagnostic techniques. Part 3 will review therapeutic techniques, particularly those involving lasers. Data from ISI®'s *Science Citation Index*® are used to trace some of the important developments in medical diagnosis and treatment. The advantages (and some attendant problems) of noninvasive approaches will also be discussed.

## What Is Noninvasive Medicine?

Though the term "noninvasive" appears in many titles and texts of medical and clinical research papers, the concept itself has not been defined or discussed at any length in the literature. *Webster's* defines the term as "not involving penetration (as by surgery or hypodermic needle) of the skin of the intact organism."[2] Taken literally, this would limit medical therapies to those not requiring injection of medication or other substances. Unfortunately, most health problems still require more than just a pill or potion.

"Noninvasive" as used in the medical literature, on the other hand, refers to a range of medical techniques and approaches—diagnostic and therapeutic. Medical usage suggests a continuum of procedures differing in their *degree* of invasiveness—with conventional surgery at one end and atraumatic healing at the other.

Table 1 presents the spectrum of medical interventions on a scale of noninvasiveness—with trauma as a primary factor. An alternative scale could be constructed with "recovery time" as the main criterion for

**Table 1:** **Proposed scale of noninvasiveness.** Examples are mostly from diagnostic and therapeutic techniques covered in this essay.

| LARGE INCISIONS | SMALLER INCISIONS | MINOR INCISIONS | NO INCISIONS |
|---|---|---|---|
| ***Components*** | | | |
| • great trauma to skin; many stitches; use of scalpel | • less trauma to skin; minimal stitching or only clips, clamps; brief use of scalpel | • some trauma to skin; no stitches; use of puncturing instruments (catheters, guiding wires, fiber-optic probes) | • little or no trauma to skin; no stitches; no probes (except needles) |
| • general or regional anesthesia | • general or local anesthesia | • local anesthesia | • generally no anesthesia (sometimes local, for therapeutic procedures) |
| • inpatient setting (operating room) | • inpatient/outpatient setting (operating room or ambulatory surgery) | • outpatient setting (ambulatory surgery or doctor's office) | • outpatient setting (hospital, clinic, or doctor's office) |
| • high morbidity; long post-operative recovery | • lower morbidity; shorter postoperative recovery | • low morbidity; brief post-operative recovery | • no morbidity; no recovery period<br>• infusion of dyes and radioactive tracers (for imaging purposes) |
| ***Examples*** | | | |
| • aortocoronary bypass surgery<br>• hysterectomy; laparotomy<br>• nephrotomy | • angioscopy; venous cutdown and cannulation<br>• hysteroscopy; laparoscopy<br>• lithotriptoscopy | • balloon angioplasty; laser angioplasty<br>• cyst aspiration; endometrial biopsy<br>• percutaneous nephrostolithotomy<br>• photodynamic therapy (in treatment of cancer) | • CT scans; MRI; PET; X rays; ultrasonography; DSA; electrocardiography; EEG or MEG<br>• extracorporeal shock-wave lithotripsy; photopheresis; electrical stimulation (in treatment of scoliosis, etc.) |

gauging the invasiveness of a procedure.[3] Thus, at one end of the scale is conventional surgery, with its attendant morbidity (pain, risks, and lengthy convalescence). This class of surgery invariably requires a fairly large incision and general anesthesia. At the other extreme, and discussed in Part 1, are the nonintrusive interventions of neurostimulation, acupuncture, hypnosis, and behavioral strategies. These have been used to manage or prevent pain as well as to cure disease. As the diagram indicates, this end of the spectrum generally involves diagnosis and treatment without medication and, more important, without trauma and risk of complications. All other medical interventions fit somewhere between these two extremes. For example, as will be discussed in Part 3, surgical procedures that use lasers are most often done percutaneously (through the skin). They involve only a small incision (generally not requiring stitches) and local or, at most, regional anesthesia. Further to the right are diagnostic and therapeutic techniques that require no incisions and that have essentially replaced exploratory surgery.

This rough taxonomy of noninvasive medical techniques, then, charts the course of painless medicine. A few diagnostic techniques will be discussed in these terms.

## Noninvasive Diagnostic Techniques

Due to space limitations, a detailed description of all current diagnostic techniques is not possible. Many of these technologies were mentioned in a previous essay, though from a different perspective.[4] The following is a selection of the most promising technologies, as reflected in ISI's database, and particularly in our research-front data. To "see" into the body with minimal physiological and morphological disturbance is the aim of all recent noninvasive diagnostic imaging techniques.

Although research in diagnostic imaging has spanned more than four decades, it was the advent of modern computers in the 1970s

| PARENTERAL MEDICATION | UNDER/OVER SKIN APPLICATIONS | NONPARENTERAL MEDICATION | NO MEDICATION |
|---|---|---|---|
| • little trauma to skin; great psychic or venous trauma; skin puncture with needle | • little trauma to skin (except for minor skin irritation) | • no trauma to skin | • no (or negligible) trauma to skin |
| • sometimes topical; generally no anesthesia | • no anesthesia (except initially, to install subcutaneous pump) | • no anesthesia | • no anesthesia |
| • outpatient setting (clinic or doctor's office); home setting | • outpatient setting (clinic or doctor's office); work or home setting | • home setting | • outpatient setting (clinic or doctor's office); home setting |
| • minimal morbidity (confined to injection site) | • no morbidity (except for mild skin irritation) | • no morbidity (except for irritation of mucous membranes or of GI tract) | • no morbidity<br>• no drugs |
| • injection of radionuclides (for diagnostic imaging)<br>• blood aspiration (for testing)<br>• chemotherapy through vein<br>• intramuscular or subcutaneous injection of medication | • electrodes, transducers, etc. (for diagnostic tests)<br>• insulin pumps<br>• infusion ports (for chemotherapy, blood aspiration, etc.)<br>• slow release drugs (via skin or buccal patches) | • inhalation of radionuclides (for diagnostic tests)<br>• insulin nasal spray<br>• cytotoxic pills<br>• ingestible spansules | • history taking; physical examination (for diagnosis)<br>• transcutaneous electrical nerve stimulation<br>• acupuncture<br>• hypnosis<br>• behavioral strategies |

that made a new generation of imaging systems feasible. These include digital radiography (of which digital subtraction angiography, or DSA, is a prime example), X-ray transmission computed tomography (CT), radionuclide emission tomography (of which positron emission tomography, or PET, and single photon emission computed tomography, or SPECT, are good examples), ultrasound, and magnetic resonance imaging (MRI). As Richard A. Robb, Department of Physiology and Biophysics, Mayo Clinic, Rochester, Minnesota, states, all have the following unique capability: "to produce noninvasively accurate numerical representations of the distributions of various structures and/or functional processes within the body."[5]

## Computed Tomography

CT, or computed axial tomography, is perhaps the most widely known and used of the new digital radiographic techniques. Developed in the early 1970s, CT scanners convert X-ray pictures into digital computer code to make high-resolution images. CT scanning thus consists of two sequential processes. First, X-ray absorption data within a single cross-sectional plane are acquired. Second, these data become the input for a computer, which uses the data (through the solution of a series of complex equations) to display an image. As James D. Meindl, director, Stanford Electronics Laboratories, Stanford University, California, explains, CT "images a transverse plane through the body similar to a section that might be made by a knife cut through a cadaver." In other words, "CT imaging presents a new vision of anatomic detail during life." This technique differs from conventional X-ray imaging, which "projects all anatomy between the x-ray source and the film plate detector into a single image."[6]

Among the virtues of the CT scanner over conventional radiology are its ability to detect very minor differences between normal and abnormal tissue and its imaging of organs without overlying tissue. It also involves a smaller overall radiation dosage to the patient. Recent developments in CT include the three-dimensional construction of multiplanar images. For example, G.T. Herman, Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, reports on an inexpensive approach to three-dimensional imaging—using software that runs on the scanner's computer.[7]

### Ultrasound and MRI

Of course, some imaging modalities, such as digital radiography and CT, do entail some "invasion"—sometimes in the form of contrast medium injections, as well as in the form of radiation.[8] Nuclear techniques (such as PET) also use radiopharmaceuticals, but in very small doses. These techniques deliver less radiation than do radiography and CT. At the other end of the imaging spectrum, ultrasound and MRI are truly nondestructive. Ultrasound imaging is, in fact, the only modality deemed safe enough for routine use on pregnant women.

Sonography, which was developed during World War II and put to medical purposes in the early 1950s, uses high-frequency sound waves. Echoes of these sound waves are translated into signals by a transducer passed over the skin. The signals are then processed by a computer into a video image. Ultrasonographic diagnosis has been put to many uses. For example, in a 1984 paper, M. Gene Bond *et al.*, Bowman Gray School of Medicine, Wake Forest University Medical Center, Winston-Salem, North Carolina, reported on the reliability of their ultrasound system (B-mode ultrasound) in detecting and measuring plaque in the carotid arteries before it grows thick and hard.[9] Bond, interviewed in 1984, envisioned the time when what he calls "a noninvasive autopsy—in effect, exploratory surgery without incisions or probes inside the body—will be done routinely."[10]

MRI was developed in 1974. A computer translates the signals emitted from the patient's body, which is placed in a magnetic field, into an image of the area scanned. The image reflects the distribution of hydrogen atoms and their interaction with surrounding tissue. Among its uses are detecting lesions of multiple sclerosis on the brain, locating and diagnosing tumors, and examining the spinal cord. As Alexander R. Margulis, Department of Radiology, University of California, San Francisco (UCSF), explains, MRI is perhaps the most promising of all, in that it shares the advantages of all other imaging modalities without their disadvantages.[11] Like CT, it provides excellent spatial resolution; like nuclear medicine, it follows the body's metabolic processes; and, like ultrasound, it gives much tissue information and is nonionizing. This technique does have some limitations, as pointed out by Richard D. White and colleagues, Department of Radiology, UCSF Medical Center.[12] Because of the strong magnetic fields produced by the machine, MRI cannot be used on patients with cardiac pacemakers and various other implanted devices or on those who are connected to life-support equipment. All of the above imaging systems are the subjects of numerous research fronts, discussed later.

### Nonimaging Diagnostic Techniques

While the majority of noninvasive diagnostic techniques involve imaging systems, there are other procedures that evaluate body functions without the aid of images. For example, nuclear magnetic resonance (NMR) spectroscopy can "investigate the biochemical energetics of human tissues and organs noninvasively."[13] According to George K. Radda, Department of Biochemistry, University of Oxford, UK, spectra can now be generated that accurately represent the biochemistry of human organs, including the brain, liver, heart, and kidney.[13] NMR spectroscopy has, in fact, uncovered muscle disorders and metabolic abnormalities that previously could not have been detected.

Additionally, there is an array of simple blood-flow and heart-monitoring machines. Among these is a portable laser Doppler instrument, described by Gert E. Nilsson and colleagues, Department of Biomedical Engineering, Linköping University, Sweden.[14] This device allows the continuous and accurate measurement of tissue blood flow. It does so by illuminating the skin and inferring flow by measuring velocity. Another common diagnostic method in cardiology is exercise electrocardiography.[15] This technique is perceived by some as being less useful than other tests (such as echocardiography and radionuclide imaging), as technically complex, and as dangerous. These perceptions are addressed in a recent review on electrocardiographic mapping by David M. Mirvis, Department of Medicine, University of Tennessee, Memphis. The author cites numerous studies that demonstrate the feasibility and diagnostic sensitivity of this technique for investigating myocardial infarction and exercise stress testing. According to Mirvis, then, "Electrocardiography...can be performed repeatedly in any office by personnel with little technical training in a totally noninvasive manner at a relatively low cost."[16] Another technique, known as mechanocardiology, also assesses myocardial function noninvasively. A "graphic recording of all externally registered low frequency pulsations due to the action of the heart,"[17] this method too is considered less expensive and time-consuming than other cardiographic procedures.

Also reported recently, by D.A.J. Walker and W.S. Nimmo, Department of Anesthesia, University of Sheffield, UK, is a way of monitoring gastric emptying during anesthesia.[18] This method involves adhesive electrodes, which, placed on the front and back of the abdomen, measure electrical impedance of a test meal that has electrical conductivity. The output signal is then displayed on a chart recorder. Unlike other methods reviewed, this technique is noninvasive, nonradioactive, relatively portable, and repeatable. Also recently reported, in *Lancet*, is a very different diagnostic procedure used to obtain DNA for gene analysis from buccal samples (inner cheek cells obtained by mouthwash) or hair follicles, instead of from blood samples.[19]

## Research-Front Data on Diagnostic Techniques

Table 2 shows 1987 research fronts on current diagnostic techniques, especially those involving imaging. This list provides an indication of the "hottest" areas of research in diagnostic imaging systems. For example, the theoretical and applied aspects of MRI are the focus of "Methodology and medical applications of MRI" (#87-5211). One of the core papers, cited about 315 times since its publication in 1980, is by W.A. Edelstein *et al.*, Department of Biomedical Physics and Bioengineering, University of Aberdeen, UK. The authors present a new NMR technique, which they call "spin warp imaging," and give examples of its application to whole-body imaging. They also discuss optimal imaging parameters for the greatest contrast among soft tissues.[20]

A much larger front, "MRI in cardiology and head injuries" (#87-0202), with 478 papers published in 1987, deals with MRI diagnostic technology and its varied clinical applications, including cardiology and head injury. Among its 59 core papers is one by Michael T. McNamara *et al.*, Radiology Department, Division of Cardiology, UCSF Medical Center. It studies MRI's capability in detecting and characterizing alterations in signal intensity in acutely infarcted myocardium.[21]

PET, with its diagnostic capabilities, is covered in "Clinical utility of positron emission tomography" (#87-0218). Among this front's core papers are several that deal with

**Table 2: Noninvasive diagnostic techniques.** A = number of core papers and B = number of published papers in 1987 *SCI® /SSCI®* research fronts.

| Number | Name | A | B |
|---|---|---|---|
| **COMPUTED TOMOGRAPHY** | | | |
| 87-0218 | Clinical utility of positron emission tomography | 53 | 816 |
| 87-1424 | Emission and transmission tomography algorithms and techniques | 36 | 295 |
| 87-2366 | Computed tomography evaluation of pulmonary nodules | 7 | 45 |
| 87-2398 | Ultrasound and computed tomographic evaluation in renal disease | 2 | 17 |
| 87-3542 | Three-dimensional computed tomography of craniofacial deformities | 4 | 21 |
| 87-5281 | Computed tomography brain imaging | 12 | 83 |
| 87-5699 | Emission tomography in the investigation of dementia | 2 | 38 |
| **DIAGNOSTIC ULTRASONOGRAPHY** | | | |
| 87-0018 | Transcranial Doppler ultrasound | 6 | 38 |
| 87-0022 | Doppler echocardiography | 17 | 169 |
| 87-0352 | Laser Doppler flowmetry | 13 | 108 |
| 87-0560 | Fetal echocardiography and Doppler ultrasound | 16 | 106 |
| 87-2161 | Ultrasonography in diffuse liver disease | 6 | 36 |
| 87-2398 | Ultrasound and computed tomographic evaluation in renal disease | 2 | 17 |
| 87-2628 | Scrotal ultrasonography | 10 | 44 |
| 87-2703 | Scanning of the internal carotid artery and pulsed Doppler sonography | 3 | 22 |
| 87-2921 | Doppler color flow mapping and two-dimensional echocardiography | 14 | 75 |
| 87-4314 | Two-dimensional echocardiography and cardiac tomography | 3 | 18 |
| 87-4973 | Ultrasonography of rectal carcinoma | 6 | 43 |
| **MAGNETIC RESONANCE IMAGING** | | | |
| 87-0202 | MRI in cardiology and head injuries | 59 | 478 |
| 87-0381 | MRI of the musculoskeletal system | 50 | 340 |
| 87-0453 | MRI in Alzheimer's disease, vascular dementia, and multiple sclerosis | 54 | 789 |
| 87-1067 | Methodology and medical aspects of MRI | 29 | 183 |
| 87-1414 | MRI in ophthalmology | 28 | 171 |
| 87-1453 | Tumor identification with magnetic resonance tomography | 17 | 97 |
| 87-2839 | MRI in lymphoma | 3 | 19 |
| 87-3032 | Photodynamic enhancement of tumors in MRI | 5 | 39 |
| 87-3491 | Risks and artifacts during magnetic resonance tomography | 3 | 27 |
| 87-5211 | Methodology and medical applications of MRI | 3 | 60 |
| **DIGITAL SUBTRACTION ANGIOGRAPHY** | | | |
| 87-0705 | Clinical evaluation of digital radiography techniques | 11 | 68 |
| 87-0998 | Intravenous digital subtraction angiography | 11 | 65 |
| 87-3365 | Digital radiography in coronary disease | 10 | 125 |
| 87-5485 | Intravenous digital subtraction angiography in cerebrovascular disease | 3 | 24 |
| 87-6291 | Bony defect diagnosis using computerized subtraction radiography | 2 | 12 |
| **IMAGING TECHNIQUES—EVALUATION** | | | |
| 87-3918 | Nonmammographic breast imaging techniques | 2 | 13 |
| 87-5036 | Evaluation and comparison of imaging techniques | 6 | 72 |
| **OTHER (NONIMAGING) DIAGNOSTIC TECHNIQUES** | | | |
| 87-3642 | Signal-averaged electrocardiogram as a screening test | 6 | 41 |
| 87-4102 | Transcutaneous oxygen measurement | 15 | 84 |
| 87-5154 | Body surface electrocardiographic mapping | 6 | 46 |
| 87-5575 | Intraluminal pH-metry in man | 2 | 27 |

PET in the examination of cerebral function. A 1977 paper, by L. Sokoloff *et al.*, Laboratory of Cerebral Metabolism, National Institute of Mental Health, Bethesda, Maryland, has been cited in over 1,560 articles. It discusses the measurement of glucose in the various structural and functional components of the brain *in vivo*. After experimenting with a new labeling technique in which glucose is tagged with a radioactive isotope before injection into albino rats, the authors suggest that, with the development of PET, this method can also be applied to man.[22] A later paper, by M.E. Phelps *et al.*, Division of Nuclear Medicine, University of California School of Medicine, Los Angeles, proposes a model for the measurement of local cerebral metabolic rate for glucose in humans. This is an extension of the model developed two years earlier by Sokoloff and colleagues. Phelps draws attention to a general approach referred to as "physiological tomography" and points out that PET can be used not only to measure the metabolic rate of glucose, but also to measure the kinetic rate constants of the tracer element they had synthesized.[23]

It should be noted, however, that PET is too specialized and expensive to ever become widely available. As pointed out by Stanley Baum, chairman, Department of Radiology, Hospital of the University of Pennsylvania, SPECT is a more realistic alternative for smaller facilities. It uses a single photon (and therefore does not require a cyclotron on-site) and commercially available radioisotopes.[24] This view is shared by Nancy C. Andreasen, Department of Psychiatry, University of Iowa College of Medicine, Iowa City, in a fascinating review of brain imaging techniques. While conceding that PET is the most elegant of the available brain imaging techniques, she considers SPECT to be a practicable alternative for many clinical and research applications.[25]

Table 2 contains another large research front, on the use of MRI in assessing geriatric brain and cognitive disorders—"MRI in Alzheimer's disease, vascular dementia, and multiple sclerosis" (#87-0453). Many of its core papers are concerned with defining and standardizing criteria for the clinical diagnosis of brain disorders. Before MRI, clinical evaluation depended on diverse tests (in the form of questions posed to the patient) to measure mental functions. These were generally time-consuming, expensive, and unreliable, as Marshal F. Folstein and coworkers, Department of Psychiatry, New York Hospital-Cornell Medical Center, Westchester Division, White Plains, explain.[26] Also, before MRI, it was only at autopsy that the specific cause of brain degeneration could be confirmed—by brain weight and the distribution of visible cerebral atrophy. This is indicated in a 1970 paper by B.E. Tomlinson and colleagues, Department of Pathology, Newcastle General Hospital, Newcastle upon Tyne, UK.[27]

With the introduction of MRI into medicine, it is now possible to obtain what neurologist Charles M. Poser *et al.*, Boston University School of Medicine, Massachusetts, term "paraclinical evidence" of brain lesions and other central nervous system abnormalities.[28] As Guy McKhann *et al.*, Johns Hopkins University Medical School, Baltimore, Maryland, also remark, while dementia can be diagnosed only on the basis of behavior, the specific *causes* may be identified by laboratory instruments. McKhann thus concludes that MRI "reveals the demarcation of gray and white matter of the brain.... It has potential for differentiating between Alzheimer's disease, multi-infarct dementia, and low-pressure hydrocephalus."[29]

Another smaller MRI area is "Tumor identification with magnetic resonance tomography" (#87-1453). One of this front's 97 current papers (all published in 1987), by I. Shapiro *et al.*, Department of Biochemistry, Haifa Medical Center, Israel, demonstrates the potential of MRI in characterizing gynecological malignancies.[30] Among this front's 17 core papers are 4 by Hedvig Hricak and colleagues, Department of Radiology, UCSF Medical Center.[31-34] All four are evaluative studies of the efficacy of MRI in the diagnosis of pelvic tumors. The most recent of these, published in 1986, reviews MRI in gynecological oncology and the distinct advantages it offers over ultrasound and CT. For example, MRI is able to depict a tumor and to provide greater contrast between malignant and normal tissues.[31]

As mentioned earlier, together with MRI, ultrasound offers the least destructive diagnostic method. This can be corroborated by another research front in Table 2, "Scanning of the internal carotid artery and pulsed Doppler sonography" (#87-2703). Two current published papers—one by Stephen L.

Hill *et al.*, Community Hospital of Roanoke Valley, Virginia,[35] and the other by William M. Blackshear *et al.*, University of South Florida College of Medicine, Tampa[36]—describe the use of a combination of tests and machines, including duplex scanning, continuous wave Doppler signals, and pulsed Doppler ultrasonic arteriography, to detect and measure carotid stenosis. Two of this front's three core papers were published nearly 10 years ago by Blackshear *et al.*, then of the Departments of Surgery and Bioengineering, University of Washington, Seattle. Both papers, with over 160 and 90 cites, respectively, investigate the use of ultrasonic duplex scanning (to provide real-time arterial images), pulsed Doppler (to produce a flow map), and spectrum analysis (to interpret it)—all in an effort to accurately detect high-grade stenosis of the carotid artery.[37,38]

## Conclusion

The sampling of noninvasive diagnostic modalities above clearly indicates the growing sophistication of medical diagnosis. According to physician Ray Fish, who writes regularly in *Radio-Electronics*, "The real nitty-gritty of medicine remains *diagnosis*: the sifting and focusing of hundreds, possibly thousands of bits and pieces of information."[39] Computed imaging (and non-imaging) systems are enabling doctors to diagnose disease more accurately and quickly. However, many physicians believe, and rightly so, that the most noninvasive—and cost-effective—diagnostic technique remains the traditional one of listening carefully to the patient.[40] The *art* of medicine, in what is termed the Hippocratic tradition, lies in the doctor's intuition and sensitivity to the patient's overall physical and mental condition, as well as to the immediate complaints brought forth. Given this point of view, current diagnostic systems should act as adjuncts, as means of confirming what the physician already knows and of aiding in subsequent treatment decisions. Next week, in the concluding part of this three-part essay, we shall discuss therapeutic procedures and the progress made in noninvasive medicine.

* * * * *

*My thanks to C.J. Fiscus and Sanaa Sharnoubi for their help in the preparation of this essay.*




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