IATROGENESIS:
JUST WHAT THE DOCTOR ORDERED

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May 1978
The Rand Paper Series

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Santa Monica, California 90406
SUMMARY

Iatrogenesis can be considered under four classes: conscious risk; unexpected complications; over-zealous care and inept care. This paper addresses the first three classes and presents examples in the area of drug therapy, surgery, coronary care units, and medical screening.
ACKNOWLEDGEMENTS

A version of this paper will appear as a chapter in Preventive Medicine and Public Health, 11th edition (J. M. Last, editor).
IATROGENESIS
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"Iatrogenesis" refers to the production of disease by the manner, diagnosis or treatment of a physician or surgeon. (For our purposes we will acknowledge the growing size of the health care team by extending this definition to include the full range of "iatrists".) There are some who are prepared to indict medical care in its entirety as iatrogenic, claiming at best it is addictive and, at worst, dangerous.\textsuperscript{1,2} This paper promises neither panaceas nor wholesale indictments. We are not creating a scorecard on the overall success of medical care, but rather focusing attention on one aspect and its implications. Perhaps we need a new Surgeon General's warning about the potential hazards of such concerns to one's peace of mind.

We must recall that disasters make the news. Good outcomes do not get the same publicity. When we look at the denominator—the rate at which people are exposed to potent medical innovations—we may conclude that things are much better than we thought. However, in terms of volume alone, we are awash in iatrogenesis. A computerized listing of medical journal citations on iatrogenic reports on surgery and drugs over a 30-month period undovered almost 200 articles. They read like a shelf of gothic novels, a testimony to Murphy's law.

One dramatic description of the extent of iatrogenic illness notes that the number of deaths and nonfatal hospitalizations directly attributable to medical intervention equals or exceeds the average number of deaths and nonfatal casualties from either the Korean or Vietnam wars.\textsuperscript{3}

Medical care represents a balancing of alternatives not unlike the second law of thermodynamics: For every action we take there is a risk (reaction). Each therapy carries the danger of producing some untoward effect—a side effect, an excessive dosage. The possibility of benefit must be weighed against the physiologic cost of treatment. In a technologically sophisticated society, the line between doing good and causing harm may become very fine. Each time we identify an illness
we intervene in the patient's life, changing his status and sometimes his entire lifestyle. If iatrogenesis is considered the production of morbidity through treatment, then iatrogenesis is ubiquitous; it is a part of every step of medical care. The salient issue is not whether iatrogenesis occurs or how it can be avoided, but rather how it can be identified and minimized.

This paper will examine the range of iatrogenic disorders from the more obvious consequences of drug therapy and surgery to the more subtle problems of diagnosis, labeling and general excess zeal. Iatrogenesis quickly raises issues of ethics and effectiveness that are discussed elsewhere. Our focus here will be to illustrate the dimensions of the problem and to suggest some ways by which it can be alleviated.

For purposes of this discussion, we will consider four classes of iatrogenesis:

1. **Conscious risk** - as indicated, many diagnostic and therapeutic decisions require the therapist to choose a method that carries some known amount of risk. Each surgical procedure and most drugs fall into this category.

2. **Unexpected complications** - even when care is provided according to the best established techniques, a complication may arise. For example, an exploratory laparotomy may provoke an undiagnosed aneurysm to rupture, or a drug may have a long-term side effect previously unknown.

3. **Inept care** - errors of judgment, lack of skill, inadequate knowledge or superficial attention can lead to disastrous consequences. There is no excuse for poor or neglectful care, be it mis-diagnosis, improper treatment, or inadequate nursing care. Nor do we condone, in any form, the charlatan with his nostrums and miracle remedies.

4. **Overzealous care** - the creation of dependency is a dangerous side effect. Inadequate concern about the psychological aspects of illness can be as crippling as physical ones. So, too, can one produce economic cripples—individuals and whole
societies. Poverty may soon become a side effect of medical care. The choice of an expensive treatment form (e.g., hospital) when a substantially less costly and equally effective alternative is available represents one way in which medical care can lead to excessive utilization of resources. Simpler examples like the choice of antibiotics and excessive diagnostic testing come easily to mind.

As seen in these examples, the most common areas of concern deal with therapy, particularly surgery and drugs; but diagnostic activities also take their toll. We will look first at some of the ways in which drugs may be associated with iatrogenesis.

Drugs

Drugs are ubiquitous poisons. It is estimated that 75 million adult Americans take an average of 2.0 drugs regularly (at least once a week and usually daily). Over 15 million people take aspirin regularly; 10 million regularly use anti-hypertensives; over 5 million are on oral contraceptives, tranquilizers or antacids. 4

The utility of a drug depends upon its correct usage for the proper conditions in the correct amounts. Even when used correctly, drugs may have untoward effects that we accept as part of the cost of therapy. Despite an active regulatory process which requires a great deal of testing at both the clinical and animal level, drugs are released only to discover that they cause serious problems when used in broad populations. 5 The association between deep vein thrombosis and the use of estrogenic birth control pills is one such example. Sometimes the relationship may take a long time before it becomes apparent. Tranquilizers taken by pregnant women can produce deformed babies. Estrogens given to a mother may lead to a higher rate of vaginal cancer in the child. The deleterious effects can be very subtle. Long exposure may be required as seen in the postulated

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*Occasionally, just the reverse may occur, as with the unexpected reduction in incidence of rheumatoid arthritis associated with the use of oral contraceptives 5 or the protective effect of aspirin on myocardial infarction. 6
relationship between sustained use of reserpine and the increased incidence of breast cancer.\textsuperscript{7}

One controversy that continues to rage is the report of the University Diabetics Group Project which claims to have shown a significantly increased rate of coronary deaths in patients using oral hypoglycemic agents.\textsuperscript{8,9} Critics of the study have attacked everything from its design to the role of the Food & Drug Administration\textsuperscript{10} but, at the very least, the UDGP leaves us with a high level of anxiety about the dangers of what had first seemed a pharmacologic breakthrough.

More commonly, drugs are used where we know the side effects and must weigh the possible benefit against these unpleasant actions. With proper precautions, we may trade a little sleepiness for temporary relief of cold symptoms. The effort to kill tumor cells leaves a wake of destruction and anguish in the bodies of cancer victims. It is indeed difficult to know when the therapy is worse than the disease.

Jick\textsuperscript{11} has developed a paradigm for the alternative strategies appropriate to different prevalence rates of the complication and the illness, respectively. Drug-related complications are a major problem. Data from the Boston Collaborative Drug Surveillance Program suggest that almost one-third of hospitalized patients experience at least one adverse drug reaction during hospitalization and that about three percent of hospital admissions to general medical services are due to adverse drug reactions. Drug-attributed deaths occur in only 0.3 percent of hospitalized medical patients.\textsuperscript{4}

Drugs may be misused. The misuse can result from ignorance or it can be a deliberate variation with accepted practice. The use of amphetamines as stimulants and anorectic agents is a flagrant example of the latter. The former is more difficult to identify and control. A recent survey suggests that there is a variation in knowledge about some common drugs and their uses.\textsuperscript{12} Some quality of care studies have uncovered inappropriate use of drugs like antibiotics.\textsuperscript{13,14} Other, even more potent drugs, are likely misused as well. Aside from
narcotics, no special requirements beyond a medical license are imposed on physicians using even the most sophisticated drugs. The general practitioner can prescribe powerful anti-cancer regimens. One proposal that has appeared from time to time is a limitation on the right to prescribe certain classes of drugs according to speciality training or other evidence of special preparation. The alternatives appear to be a continuation of the current laissez-faire approach or a retrospective surveillance with subsequent revocation of privileges for persistent offenders—neither of which is particularly attractive.

Perhaps the most common form of drug abuse is the excessive use of many forms of drugs without adequate justification. The most commonly misused prescription drugs are tranquilizers and antibiotics. The former constitute the most frequently used drugs and are liable to be prescribed indiscriminantly and continued almost indefinitely. We have, as a result, produced a national epidemic of drug addiction, perhaps far more dangerous than the illicit drug trade we hear so much about.

It is ironic that concern over addiction may also produce iatrogenic pain and suffering. In the case of the terminally ill, addictive narcotics may be dispensed too parsimoniously because of an irrational fear of creating addicts of persons expected to live only a few months.

Antibiotics are too often prescribed without adequate justification, frequently for illnesses where they are ineffective (e.g., viral infections). The results of widespread excessive drug use may have environmental effects as well as individual ones. The most obvious is the problem of drug-resistant organisms associated with indiscriminate use of antibiotics. We may not yet appreciate the full range of environmental impact of the generously prescribed, potent medications we see in common use. The carcinogenic effects of hormones in cattle and humans are beginning to be recognized. Fears of genetic disturbances, precipitated by newer pharmacologic agents from psychoactive drugs to enzyme-inducing agents, have already begun to surface.
In some instances the issue of whether or not to employ a particular therapy is unresolved. Conflicting data are presented and the line between benefit and harm is difficult to draw. A case in point is the use of anticoagulants in the management of myocardial infarction. We have seen a waxing and waning of enthusiasm. A recent compilation of controlled trials suggests that they are beneficial, but the diffusion into practice of a consistent, rational policy after the heat of debate is uncertain.

Surgery

Many of the dilemmas of the prescription pad have their parallel in the scalpel. There is a basic risk of surgery associated with the use of general anesthesia (approximately one death per 1000 anesthetic inductions) and there are specific risks associated with various operations. There are those who claim we are too quick to operate and those who feel we are indiscriminate. Beyond operative mortality, the complications from surgery include both the direct effects of organ disruption and secondary effects on physical and psychological functioning.

The relative benefit of surgical intervention has been subjected to more careful scrutiny of late. More sophisticated techniques of cost-effectiveness analysis provide provocative data to dampen our enthusiasm for many elective surgical procedures. Surgical rates in the United States are substantially higher than those observed elsewhere but it is not always clear how that information should be interpreted. For example, the families of physicians show a higher rate of elective surgical procedures than a comparable group of families of other professionals. Within regions there is a wide variation in elective surgery rates. No consistent patterns can be demonstrated to relate the variation in surgical rates with either precipitating morbidity, availability of resources or different standards for selecting patients. However, the fact of the variation is seen as presumptive evidence that at least some proportion of the higher rates represent excesses.
McCarthy and his colleagues have introduced a technique designed specifically to identify this potentially unnecessary elective surgery and prevent it—the second opinion. Whether offered as a voluntary option or a mandatory requirement, a second surgeon's opinion on the need for elective surgery identified a substantial number of patients for whom the need for the procedure was not confirmed. In the initial studies, the non-confirmation rates were 30 percent for the voluntary group and 18 percent for the mandatory group.\textsuperscript{24,25} At present there is still no data on the relative morbidity of either the 19 percent of those people (with recommendations against surgery) who, nonetheless, elected to have the surgery or on the 27 percent of people who were confirmed for surgery, but decided against it.

It is important to appreciate that this type of pre-surgical screening depends upon the implicit judgment of the surgeon, be he rendering a first or second opinion. In many (if not most) instances, we lack the clear-cut criteria to indicate when a surgical procedure should be performed.

In some instances the controversy may focus on the efficacy of the procedure itself. Currently the place of coronary bypass surgery is caught up in such heated debate. The past decade has witnessed growing enthusiasm for direct surgical intervention on blocked coronary vessels. Growing lists of case reports enthusiastically testify to the beneficial results of the bypass procedure. But there is growing recognition of the need for more significantly controlled trials of new therapies, even in surgery.\textsuperscript{26} As a result, a multi-center cooperative trial was initiated in the Veterans' Administration hospital system.\textsuperscript{27} The early reports from this project indicate no significant difference in mortality or morbidity among victims of persistent angina pectoris who have been treated surgically or medically.\textsuperscript{28}

Not surprisingly, the reactions to these reports have been heated.\textsuperscript{29-31} Vigorous proponents of bypass surgery argue that the organized trial does not use the best surgery and that inter-surgeon variation is important. The conservative medical group hints that even the positive results of surgery seen could be based in substantial measure
on placebo effects. They cite a previous study of surgery for coronary artery disease in which the very exciting positive results initially reported for the procedure were eventually shown to be no greater than those achieved in a sham operation.32

Meanwhile, the patient is left in the middle. The operation is expensive and debilitating. It carries an operative mortality risk of 1–4 percent. At the same time, it is a treatment for a common, painful, disabling, and life-threatening condition. Everyone wants the operation to work; when, then, should a recommendation for the procedure be construed as iatrogenic?

The surgeon's capacity to mutilate implies a great responsibility. Women appear to be particularly vulnerable targets---so much so that some feminists have begun to label hysterectomy an iatrogenic disease secondary to male chauvinism.33 Whatever the etiology, the performance of hysterectomies does not seem to be highly sensitive to external forces. Relatively simple surveillance can produce substantial changes in performance rates.32

The removal of a breast is both physically and psychologically traumatic. Even beyond the implications of breast cancer itself, the disfigurement and possible loss of function in an upper extremity extract high prices from afflicted women. One would want to be very sure that there were clear advantages in survival rates from the more debilitating mastectomy procedures compared to simpler operations (perhaps in combination with other modalities such as radiation or chemotherapy). Once again, the picture is far from clear. Extensive dissection of breast tissue, lymph nodes, and attendant destruction of muscle mass has not been shown to yield consistently better survival rates than more modest surgical therapy.

Let us conclude this section with some general observations about contemporary surgery and its role in iatrogenesis. A study in the early 1960's of 34 hospitals revealed a wide variation in post-operative mortality rates ranging from 0.27 percent to 6.40 percent. This 24-fold ratio could be reduced to about a 3-fold difference when factors such as patient-mix and case-mix were
statistically controlled. Nonetheless, a difference was persistently present. The fact of this difference suggests that, even if surgery continues to be applied at its present rate, some steps are available to reduce the deleterious impact of this application. There is certainly room for improvement.

At a slightly more subtle level, there is also much room for improvement in the way we manage surgical patients. Several studies suggest that pre-operative information and support reduce stress and reduce post-operative distress. We thus have available a technology to alleviate unnecessary suffering.

Other Therapies

Our lack of consistency in treatment is not limited to the use of drugs or surgery. Witness the history to date of our management of acute myocardial infarctions. We have already noted the controversy surrounding the use of anti-coagulants, but there are even wider gaps in our knowledge. As our capacity for technologic intervention increased, the site of care has shifted increasingly to the hospital and then to specialized units within it. Perhaps nothing epitomizes this technologic revolution so well as the coronary care unit. Once again, there are a host of enthusiastic case reports extolling the value of this therapeutic breakthrough and, once again, there is a dearth of controlled studies to test the concept. By now the CCU has become standard medical practice and denial of its "benefits" to a control population is virtually unthinkable.

Nonetheless, there are reports that suggest some degree of temperance of our enthusiasm. On one hand we have studies that recount the terrible psychologic burden of patients treated in such a unit. On the other hand we have a few controlled studies to indicate that, at least for some groups of patients, home care is as effective as CCU care.

Moreover, we run the risk of inflicting disability on disease. Tremendous energies expended on the treatment of coronary heart disease may produce a cardiac cripple. Our treatment of the disease has
changed with time and fashion. A quarter of a century ago we began to move the heart attack patient from bed to chair. Now we are seeing increasing urging for early ambulation and early discharge from the hospital but no signs of consensus.

It is important to appreciate that few of these studies are based on any extensive bodies of theory. Each innovation relies on a clinical investigator's interest in pushing the bounds of accepted practice a little further on the basis of clinical intuition. Too often, studies done on highly selected populations or in rarified environments are too quickly popularized and mis-extrapolated to general patient populations. Cochrane has criticized this trail of medical "progress". He notes with distain the relatively small number of medical practices that are based on carefully performed controlled clinical trials. But even the best of experiments may be flawed by the constraints proposed by the real world. Are we prepared to declare a moratorium on the introduction of new technology (including surgery and pharmacology) until they can be subjected to extensive clinical trials and a prolonged period of careful observation for unanticipated untoward consequences. Presumably the FDA has established regulations designed to achieve such ends; their failures speak eloquently to the feasibility of such an approach.

This question of conservative versus active management of patients can be found in other aspects of medicine as well. Each time the patient is caught in the middle he risks both physiologic and psychologic trauma. Controversies continue about such issues as the value of strict control of diabetes mellitus or dietary management of peptic ulcer disease. Each urging of stricter limitations on patient behavior implies restricted lifestyle and additional stress. This may be a high price to pay for ambiguous efficacy.

In many respects, our successes breed our dilemmas. As we develop the means to artifically reproduce the function of organ systems, we create a series of moral and social problems. Who has the right to continue or to terminate life functions? When do the costs outweigh the benefits? A case in point is the treatment of chronic renal
disease. Our ability to artificially dialyze patients with chronic kidney failure imposes upon them and their families a major burden of economic, physical, social and psychological adjustments. It is not surprising that the suicide rate among such patients is high.54

Diagnosis

The physician-taxonomist is addicted to diagnosis. The process of labeling implies understanding and suggests at least a prognosis, if not a treatment. This critical care step then offers the patient reassurance that the dreaded entity is, in reality, something more benign or it may mean that the patient's whole future is blighted by the announcement of an affliction. This business of labeling is indeed a weighty responsibility.

Reviews of the degree of inter-observer variability do little to reassure us about the reliability of such clinical judgment.55 The issue of diagnostic accuracy will be examined in greater depth in the chapter on the evaluation of preventive programs, but we will explore here a few issues related to three types of diagnostic problems: false positives, false negatives, and labeling without benefit.

Bergman56 has provided dramatic evidence of the damage that can be done by too zealously detecting disease, especially in children. His description of the tragic limitation imposed on youngsters because of the presence of a heart murmur (that proved to be physiologic only) serves to remind us of just how potent a diagnosis can be.

Diagnosis can also be fickle. Perhaps no area of medicine illustrates this phenomenon so vividly as psychiatry. In one provocative study, health individuals deliberately presented themselves at mental hospitals complaining of symptoms associated with psychiatric disease. Once labeled and admitted, they could not establish their wellness despite perfectly rational behavior.57 Equally provocative, once the hoax was admitted and announced, admissions to mental hospitals dropped dramatically as physicians were now reluctant to admit such bogus patients.

A more tragic example of the price of false positives comes from the recent reports of a national breast cancer detection project. Of
some 280,000 women screened by mammography, 66 who were said to have had "minimal cancer" on biopsy were later found to have benign lesions by an expert pathology review committee; 53 of these women went on to have mastectomies. It is unrealistic to expect no error in pathologic judgments. In fact, some would argue that the 13 percent error rate in minimal cancers is surprisingly good. Other studies of inter-rater reliability among pathologists have not shown rates as good.

What is more upsetting is the implication of this report. The study alluded to was a federally financed research project with highly qualified investigators and a variety of review mechanisms. How much more likely is it, then, that far higher error rates afflict daily clinical practice?

The results of false negatives are easier to appreciate. We are all familiar with stories of patients whose illness went undetected until they presented in a terminal condition. Where a treatment for a condition is available (and especially where it is a cure), delay in treatment or failure to obtain treatment is a tragedy. Missing such a diagnosis means that the patient foregoes the chance for therapy. Unfortunately, we do not live in a black and white world. If we choose to set levels for diagnosis so as to avoid false negatives, we do so at the cost of producing more false positives.  

The final question in this section of our discussion is whether we ought to bother with diagnosis at all. There exists in medicine, as in most pursuits, a certain degree of the Mt. Everest syndrome: When asked why he climbed the mountain, an adventurer replied, "Because it is there." It is useful to pause in our enthusiasm to label and ask ourselves to what end we do it. This question is raised repeatedly in screening programs, especially multiphasic screening, where each abnormal finding may necessitate an expensive pursuit of further data. In clinical practice the identification of an individual as having a given illness for which there is no known treatment is a mixed blessing. To the extent that diagnosis can accurately predict prognosis, the clinician can provide guidance. But he does so at the cost of anxiety and disruption. A labeled individual is no longer
the same. Certain opportunities from things like life insurance and health insurance to employment may not be as readily available.

Fundamental Issues

We began this discussion by listing a set of classes of iatrogenesis. We close the presentation with a set of related questions:
1. Who should be responsible for the results of treatment?
2. What level of performance is reasonable?
3. How can iatrogenesis be monitored?
4. How can iatrogenesis be minimized?

We raise these questions in full recognition that no simple or permanent answers are feasible. The responsibility for the outcomes of care opens a Pandora's box. Issues of informed consent, patient compliance, institutional and individual licensure come quickly to mind. Certainly this question touches upon a series of ethical and legal concerns discussed elsewhere. However, it is important to recall our initial premise: Medicine is not yet, and likely never will be, an exact science. At best it represents a set of known probabilities. For the most part, we must choose between doing nothing or proceeding on the basis of insufficient data. Either choice represents a risk.

No one condones the inept practitioner or the careless one. Licensure, certification and structural requirements should be enforced to insure that such problems are eliminated. If well-trained pilots can use checklists for repetitive tasks to add an extra margin of safety, why cannot a physician? We should discourage the virtuoso showman and encourage the cautious technician.

At the same time, the practicing physician is constrained by the progress of the field in general. Patients and physicians alike may be anxious to adopt the therapeutic recommendations based on vanguard data. In many situations, it may be more prudent to delay dissemination of a new technique through means such as special licensing until adequate trials can be conducted and evaluated. At present there are few restrictions on physician behavior. State licenses to practice
medicine tend toward the permissive endorsement of "medicine and surgery in all its branches." Our only checks lie in hospital staff privileges and malpractice insurance coverage—both quite fallible.

At the same time, we are seeing an increasing trend toward advanced training and specialization. This phenomenon can provide the basis for more limited licensure based on training and demonstrated capability. Such restrictions could apply to the right to prescribe certain drugs as well as the performance of diagnostic and therapeutic procedures.

Such changes will not necessarily make physicians more aware of their responsibilities, however. We need some means of reminding the profession of its cardinal tenet; "Primum non nocere." Regulation is not likely to be effective nor can we rely on exhortation. Pragmatically, our best defense is an informed consumer who can at least inquire about the risks and implications of diagnosis and therapy. Such a solution is not likely to satisfy those in search of a foolproof safeguard, but it is probably an accurate reflection of the situation as it is and as it will be.

Finally, we must acknowledge our great need for more information. We have alluded to some of the problems of monitoring untoward reactions. Constant scrutiny and an active data retrieval system are of paramount value in this pursuit. We also need far more information about what are reasonable expectations of outcome for various treatment modalities. It will only be by studying the varying rates of successful intervention across sites that we can identify those with good results and isolate the approaches they employ in order to foster these over other means.
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