Getting in Nature's Way

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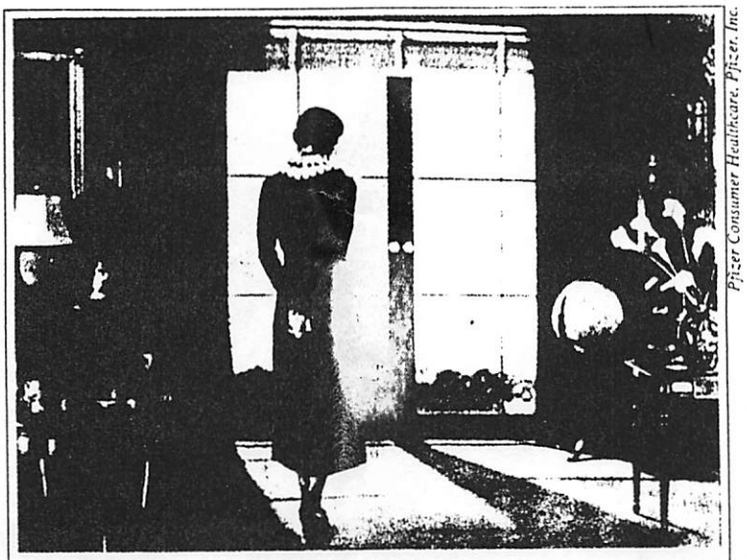
The Pursuit of Perfection: The Promise and Perils of Medical Enhancement
by Sheila M. Rothman
and David J. Rothman.
Pantheon, 304 pp., $25.00

Scientifically advanced nations, most notably the US, seem on the verge of a new situation in which the traditional goals of doctors and others concerned with health care will be radically altered. The changes will be the result of increased understanding of the basic molecular mechanisms shared by all living things and a widened ability to devise technological methods by which those processes may be manipulated. More than a few observers of the biomedical scene believe that we are about to enter an age in which the improvement of human bodies and minds will become a primary goal in research and clinical treatment. Some of these observers are hopeful; some point to the possibilities of inherent and unforeseeable danger.

Until little more than a century ago, the only aims of medical care were the cure of disease and the relief of human suffering. But the definition of "human suffering" has gradually changed. We now find ourselves faced with the reality that it is no longer sufficient to prevent or treat sickness of the body or mind, but that physicians are expected to address increasing attention—and society's dollars—to the millions who are dissatisfied with what nature and their own DNA have given them. Whether for rhinoplasty, botox injections, or a prescription for sex hormones, thousands of men and women daily make their way to doctors' offices, intent on improving themselves. Not sick in any usual definition of the word, such discontented people would like to be better than they are, better than merely well. Even "better" may not be enough. That is why Sheila and David Rothman have called their cautionary new book *The Pursuit of Perfection*.

If the pronouncements of some futurists are to be believed, enhancements of human appearance and function will soon be so effective and commonplace that many will wonder in coming years why some critics scoffed when Gregory Stock, director of the Program on Medicine, Technology and Society at UCLA, called his book *Redesigning Humans: Our Inevitable Genetic Future*.[1] The title of Stock's opening chapter was "The Last Human," by which he meant

[1]Houghton Mifflin, 2002.



Pfizer Consumer Healthcare, Pfizer, Inc.

The Menopause: Its Modern Management

From an advertisement for estrogen by Parke, Davis & Company, 1937

those few remaining whose bodies and minds have been formed by nature and nurture alone. As they age to more than double the biblical three score years and ten, the contented beneficiaries of the coming technologies may look back with scorn at the bioethicists and others who criticized William Haseltine, the biotech entrepreneur and CEO of Human Genome Sciences Incorporated, when he proclaimed to a *New York Times* reporter, "I believe our generation is the first to be able to map a possible route to individual immortality."[2]

These are the outcomes envisioned by the pioneers who believe a biogenetic gold rush will soon take place. But every new technology carries the possibility of introducing unacceptable risk as well, which is why the subtitle of the Rothmans' book is "The Promise and Perils of Medical Enhancement." The Rothmans deal not with the future, but with such recently popular treatments as hormone replacement and cosmetic surgery. Showing how these have been evaluated may help to avoid mistakes in administering treatments. We should profit, say the Rothmans, from the errors of excessive certainty, popular zeal, and self-interest that have accompanied some recent innovations. And we would profit also from a frank assessment of the sometimes deliberate and sometimes inadvertent collusion between researchers, pharmaceutical companies, and practicing physicians that has enlarged the market for enhancement.

Sheila and David Rothman are social historians of medicine whose writings have brought attention to the ways in which communal, economic, and political forces combine to influence decisions that many of us naively thought were shaped only by the needs of patients and the progress of science. Two of their books have become minor classics among bioethicists because of their careful documentation and thoughtful, if partisan, analysis of events that led to significant changes in patient care as well as attitudes toward the medical profession. In their 1984 book *The Willowbrook Wars: A Decade of Struggle for Social Justice*,[3] they described the lawsuits brought by parents against the Willowbrook State School, a home for retarded children and adults in New York City with notoriously wretched living conditions and an abusive staff. Like the inmates' parents, the Rothmans believed the inmates could cope with life on the outside more effectively than the state authorities imagined. They showed that reforms would never have taken place if parents, public organizations, and politicians had not become involved. In their view, improvements in health care policy will only take place when the public demands them. It is not from within the medical profession that reform is accomplished, but from without.

In 1991, David Rothman published *Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making*,[4] chronicling the rapid evolution, primarily between 1966 and 1976, of the doctor-patient relationship, which rendered it less paternalistic and gave patients more autonomy as it brought new participants into the process of health care. Much of the change came about as the result of the social upheavals of the late 1960s, which gave rise to increased demands for self-determination and hastened the establishment of bioethics as an academic discipline.[5] The most forceful public expression of the principles of medical self-determination occurred with the *Roe* v. *Wade* decision of 1973, prohibiting state laws that restrict a woman's right to abortion during the first trimester of pregnancy. By then, medical treatment was being influenced not only by increasingly insistent patients but by the courts, ethicists, the writings of social scientists and legal scholars, and an ever more knowledgeable public demanding to know how decisions concerning medical research and clinical care were actually being made.

Rothman argued that increasing pressures to carry out clinical research after World War II conflicted with medicine's historic commitment to the individual patient. The size of the research establishment grew enormously in the two decades following the war, as the National Institutes of Health were rapidly enlarged and the federal government poured huge amounts of money into university health centers, most of which was directed toward clinical and laboratory investigation.[6] Academic promotion came to depend far less on teaching and patient care and far more

[2]See Nicholas Wade, *Life Script: How the Human Genome Discoveries Will Transform Medicine and Enhance Your Health* (Simon and Schuster, 2001), p. 162.

[3]Harper and Row.

[4]Basic Books.

[5]See Albert R. Jonsen, *A Short History of Medical Ethics* (Oxford University Press, 2000).

[6]See Kenneth M. Ludmerer, *Time to Heal: American Medical Education from the Turn of the Century to the Era of Managed Care* (Oxford University Press, 1999).

on the publication of papers in scholarly journals. The result was a weakening of the bond between doctor and patient, filtering down from the medical school faculties to the doctors they trained. The situation was aggravated when new technology raised ethical questions about prolonging life, sometimes pitting doctors against patients. In 1976 there was public clamor over the case of Karen Ann Quinlan, a comatose young woman whose doctors refused to honor her parents' request to remove her breathing tube. They kept her alive by artificial means for thirteen months while her parents sued to be allowed to take her off the respirator.

Other developments combined to make a stranger of the doctor at the very bedside where he had once been the patient's advocate and source of reassurance: the increasingly impersonal atmosphere in hospitals, the introduction of widespread third-party payment and managed care organizations, the creation of the new field of bioethics, and the growing involvement of the courts. The doctor's influence was eroded by those newer strangers, among them ethicists, lawyers, insurers, and administrators of managed care. Though Rothman did not spell it out, each new participant in medical care brought about a further weakening of the personal responsibility of the doctor – the responsibility that was once the patient's best guarantee of the concerned care that is the single most important element in successful clinical treatment. The Rothmans recognize, moreover, in view of the complexities of modern medicine, the increasing fragmentation of the profession into specialized units. A patient may be referred to several different doctors for a single complaint.

In turning their attention to the problem of medical enhancement, the Rothmans consider yet another burden on physicians whose prime motivation has been the thoughtful care of the sick. The fact is that enhancement, whether through female hormones or liposuction, has a variable record, not only having often failed in its intention, but too frequently having exposed patients to unanticipated hazards—such as infection, increased risk of cancer, and even death – or to complications that might have been predicted if many members of the public were not so quick to accept innovation. Scientists, pharmaceutical houses, popular magazines, advertising agencies, and even clinicians themselves are carried along by the excitement of research advances and the eagerness of potential consumers, as well as by the prospect of making money. An enthusiasm takes hold that sweeps caution before it.

These influences are, in the Rothmans' words, "reinforced by a culture that prizes individual perfection and peak performance," and they are concerned about its implications for the future:

> The system, however, is out of balance, for no part of it has a stake in emphasizing or even communicating the dangers that are almost certain to accompany the innovation. . . . The record strongly suggests that technologies will emerge slowly and haltingly, some delivering benefits, others inflicting serious harm. Consumers will be compelled, personally and collectively, to make a series of exquisite choices, with very little data to guide them. . . . Healthy adults will have to calculate how much risk they are willing to accept in order to try to optimize a trait. Is it wise to undergo an intervention that promises to dramatically increase life span and disregard the risk that it might cause fatal disease and shorten life span?

It is this record of "slow and halting" innovation that the Rothmans address in their thoroughly documented and readable book. "What science creates medicine rapidly dispenses," they warn, and this uncritical acceptance by both physician and consumer is precisely the problem.

The Rothmans begin their narrative with a long and complex account of female menopause and its discontents. Not long after the discovery of hormones around the turn of the twentieth century, medical scientists began to view these chemical compounds as the basic determinants of physiological functioning. The very word – hormone – is the clue not only to their action but to the hopes for their manipulation as well, being derived from the Greek verb *hormaein*, meaning "to excite" or "set in motion." Extracts of animal testicles had already been thought (falsely, it was later shown) to restore youth and potency to aging men, and the search was soon on to discover the vital male force they contained, as well as an analogous female regenerative compound in the ovary.

When the female hormones called estrogens were identified, it seemed natural for physicians and women alike to promote their use in restoring the femininity lost following menopause. At first estrogens were prescribed to maintain youthful skin, hair, and outlook on life, and later to combat the distressing symptoms of menopause and its aftermath, such as hot flashes, insomnia, and loss of bone density. In time, statistical studies involving follow-up of many patients seemed to suggest that properly used hormone replacement therapy (HRT) would also decrease the incidence of heart disease, breast and genital tract cancer, and Alzheimer's dementia.

But no matter its other presumptive advantages, the emphasis was always on HRT's benefits in reversing, or at least holding off, the aging process. Though the women who took hormones may initially have been attracted by their effect on menopausal symptoms, most of those who continued treatment were more interested in how they looked, the texture of their skin, and the revitalization of their energies. To many of them and to their doctors as well, aging was a disease, unnecessary and henceforth treatable. If taking a few pills every day could enhance the quality of life without any dangers, as the press and television proclaimed with the wide agreement of the medical profession, why not try them out?

Some foresighted gynecologists warned that estrogen's potential for encouraging tissue growth might promote the development of cancer, but calls for specific studies of that possibility went unheeded. And then in

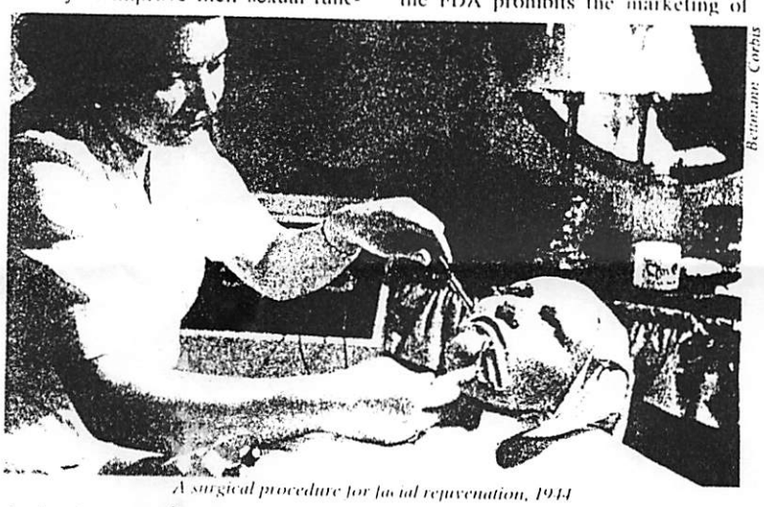
1971, it became apparent that women whose mothers had taken the synthesized estrogen compound diethyl stilbestrol (DES) during the first trimester of pregnancy had a distinctly higher risk of developing adenocarcinoma of the vagina, a relatively rare malignancy. A few years later, two studies were published describing a several-fold increase in endometrial cancer, a cancer of the uterus, among women who had been on HRT. The medical profession's response was to change the treatment, adding progesterone, a steroid hormone, and emphasizing the preventive aspects of the hormones, especially the well-documented improvement in bone density for those women at risk for osteoporosis. It is estimated that more than a third of post-menopausal American women were having hormonal therapy by the end of the 1990s. Meanwhile, further investigations had failed to confirm that it lowered the incidence of Alzheimer's disease.

Finally in July 2002, a study by the US government–funded Women's Health Initiative comparing 65,000 women on hormones to 100,000 controls was stopped because it had become obvious that those on HRT were having more coronary events, strokes, blood clots in the lung, and invasive breast cancers. Though they had fewer colorectal cancers and hip fractures than the control group, the decision about HRT was expressed as follows in an editorial in the *Journal of the American Medical Association*: "Do not use estrogen/progestin to prevent chronic disease."

Of course, there is still a place for HRT in the lives of many women who, having considered the risks and benefits with their doctor, may find it useful to take the hormones for their own distinctive physical situation. Some, for example, have such distressing menopausal symptoms that they feel justified in accepting the added possibility of danger; so do women who by family history or for some other reason are at such a high risk of developing osteoporosis that the benefits would seem to outweigh any other considerations. But at least the word has spread that such treatments do not guarantee a life of youthfulness and that decisions about chemicals whose primary purpose is enhancement must be made individually by each patient and her doctor. The real question for physicians and consumers, though, as posed by the Rothmans, is whether the kind of careful testing by the Women's Health Initiative that limited the use of HRT will be applied to other treatments. "Will they now use HRT as the model for guiding their use of plastic surgery and liposuction? Will they use the story of estrogen as a template for evaluating future genetic enhancements?"

To respond to the first question, there is no evidence that the demand for liposuction has slowed down. Over 400,000 such procedures to remove fatty tissue were performed in 2001 (of which 20 percent were done on men) and the number grows ever larger. This in spite of statistics indicating that some eighty of those patients died as a result of the operation, a mortality rate exceeding that for adult hernia repair by a factor of almost seven. Hundreds of thousands of Americans are subjecting themselves to a possibility of postoperative complications and death that surgeons would find unacceptable for any other elective procedure. It is ironic that the doctors who choose to perform an operation that is solely cosmetic are willing to accept mortality and complication rates significantly higher than those who restrict their interventions to those required for the treatment of disease. Perhaps this says something about the standards observed by cosmetic surgeons. Yet we can expect, as the authors write, that liposuction will continue to "go forward without significant attention to risks."

Ironically, the earliest of all hormonal manipulations has never established itself as either popular or particularly useful. Though hormone treatment for testosterone-deficient young men is an established medical intervention, the notion that it will rejuvenate the elderly or improve their sexual functioning has found little support in unbiased studies. Following decades of initial optimism, there seems far less interest in it on the part of either doctors or patients. One nowadays finds only infrequent glowing testimonials to testosterone of the sort that were common in women's magazines to boost the sales of HRT. There was a burst of advertising for testosterone by drug companies in the decades following World War II, but this has significantly decreased in recent years.



A surgical procedure for facial rejuvenation, 1944

Bettmann/Corbis

The reasons for the falling off of enthusiasm for testosterone supplements go beyond the fact that they have not been shown to accomplish the purpose for which they were initially touted. Because there is no male equivalent to the dramatic changes of menopause, symptoms requiring urgent amelioration—insomnia, hot flashes, weight gain, etc.—do not occur and the changes in appearance set in gradually. Moreover, middle-aged men tend not to be as intent on maintaining youthfulness, whether in appearance or physiology, as women of the same age. When they get a medical checkup, they are more likely to have it done by an internist than are women, who frequently use their gynecologist as a general practitioner. A visit to a specialist in urology, who would be far more likely to recommend testosterone therapy, only occurs if the actual symptoms overcome the man's greater reluctance to seek medical attention.

And then there is the question of cancer. Like estrogen's effect on breast tissue, testosterone can stimulate cellular proliferation in the prostate. Studies have not been extensive enough to prove an association beyond doubt, but contrary to the experience with estrogen, physicians are hesitant to prescribe a therapy with such potential when there is no proven benefit. The National Cancer Institute and the National Institute on Aging, concerned that steadily increasing use of testosterone compounds might result in a greatly heightened incidence of prostate cancer, recently asked for advice from the Institute of Medicine of the National Academy of Sciences on how to convince the public of the hormone's lack of benefit and its potential dangers. The academy has suggested small clinical trials to provide evidence of risk. Should the results of such investigations prove unrevealing, large, long-term studies could then be undertaken.

And yet, some physicians continue to prescribe male hormones. Though the FDA prohibits the marketing of testosterone as an anti-aging therapy, there are enough hints in the advertising of such products and in occasional articles appearing in the popular press that many physicians will prescribe it for selected patients. Moreover, the hormone is a staple—along with other kinds of hormones, fetal cells, and numerous antioxidants—of the hundred or more so-called "rejuvenation clinics" that have sprung up throughout the country. The result is that anyone who wants testosterone without his doctor's knowledge can get it, whether by answering an advertisement or by going on-line to a Web site that provides the names of doctors who treat "testosterone deficiency."

Among the rationalizations for giving testosterone to older men is that their natural levels of the hormone wane with age; it would seem logical to use replacement therapy even though it seems to provide no benefits. Something of the same logic has been used to justify injections of growth hormone, whose blood levels were also found to decline with the passing of years. Growth hormone treatments, often administered to children with a deficiency of the hormone, had been a source of contention for decades, not only because a number of cases of the neurologically crippling Creutzfeldt-Jakob disease were found among children to whom it was given, but also because of the vexing question of which children should receive it. Should a short but not hormone-deficient child be treated? How short is short? Where does treatment end and enhancement begin? Because the use of growth hormone in some children resulted in stronger

bones, increased muscle strength, and reduced body fat, researchers thought it might reverse some of the common problems of aging, namely osteoporosis, muscle weakness, and the accumulation of fatty tissue. Not only have the results been ambiguous, but significant side effects have occurred, such as joint pain, numbness, and swelling of the legs. In addition, experimental work indicated that mice injected with growth hormone did not live as long as those without it.

None of this has deterred the rejuvenation clinics and many physicians from prescribing growth hormone. Though not approved by the FDA to treat the symptoms of old age, there is no law against such use, and so-called "off-label" prescribing for older men is common. "All of which," conclude the Rothmans, "helps explain why enhancement technologies, whatever their putative benefits or demonstrated risks, will have significant space in our future."

And, they add, "there is no holding back the enterprise." Research will go forward, and there will be great pressure for its clinical application:

> As this history of enhancement has demonstrated time and again, routine methods of oversight will not be adequate, nor will the advice of individual physicians or professional medical societies or government regulators. What is required is an intimate understanding of the nature of the research and the reliability of the results. Only with this information at hand will consumers be able to calculate potential risks and benefits to know whether to join the line outside the doctor's office, or to demur.

This is wise advice, and the Rothmans have built a powerful case for it. But it is far more easily given than taken. In the long run knowledge guarantees neither wisdom nor sound judgment. Seeking out every available fact about some method of enhancement—or any other medical intervention, for that matter—does not give the perspective that can only come from professionally trained authorities with experience in the distinctive variety of critical thinking that is called clinical judgment. The fact that the clinical judgment of physicians has been woefully inadequate in the situations so well described by the Rothmans does not mean that it should be discarded.

What it does mean is that some of the strangers previously mentioned do have a place at the bedside. Decisions which in decades past were considered strictly clinical must now be recognized as having a moral, an ethical, a philosophical, and a legal aspect, and even a bearing on public policy. Ideally, the therapeutic implications of every coming medical advance should be scrutinized with these perspectives in mind. When that becomes the norm, society and individual patients—and the Rothmans—will need no longer fear that practitioners, medical societies, or government will abdicate their responsibility. What might be proposed for such scrutiny is a variation on today's bioethics committees, in the best of which physicians and nurses with scientific or clinical expertise join with ethicists, lawyers, the clergy, and community representatives to recommend a course of action that arises from the consensus of the group. The makeup of such committees might vary with the therapy being evaluated and its possible implications. While no system of oversight can be flawless, such committees may not only discover and publicly communicate problems that might arise with new technology but also bring attention to matters that should be considered by more specialized advisers.

The evidence that such a state of affairs may be attainable comes from American experience with end of life care. Since the Karen Ann Quinlan case in 1976, there have been many changes in the way decisions are made during every phase of the process of dying. The current wide availability of hospice care is an example of that, as are the frequent use of such legal strategies as durable power of attorney or the appointment of a health care proxy, vast improvements in palliative care, not to mention its being established as a distinct medical specialty, and the greatly increased involvement of families and patients.

In making such changes, the medical community has by and large responded with heightened sensitivity to the advice of philosophers, bioethicists, and even lawyers. My own impression is that clinicians are far more understanding, empathetic, and skilled in dealing with dying patients than they were a quarter-century ago. Pointing this out is not to imply that the demands of patients and families do not have a decisive effect, but we know that the impetus for change could not have been accomplished without the involvement of the experts and advisers I have mentioned.

I wonder whether it is true, as the Rothmans claim, that "there is no holding back the enterprise." It is just possible—now for the first time in the history of modern science—that the moment has finally come when society might reconsider whether the curiosity and enthusiasm of scientists alone should determine the direction of research into certain technologies. As biomedical investigation moves into the forms of enhancement that will affect personality, intelligence, memory, organic structure, and longevity, perhaps we ought to make use of our experience with those strangers at the bedsides, and bid them visit not only the clinic but the laboratory too.

To calculate what the Rothmans call "potential risks and benefits" is praiseworthy, but in order to do that one must have better knowledge of those risks. The misadventures that these writers portray in their important book prove that we enhance ourselves at our own peril, and much of that peril is yet to be discovered.

To accomplish the feats of genetic improvement predicted with such assurance by Gregory Stock and William Haseltine is to forget the admonition of Francis Bacon, who was, after all, the father of the scientific method: "Nature, to be commanded, must be obeyed." Two centuries earlier, Michel de Montaigne had warned of the dangers of doing otherwise when he pointed out that we should not get in nature's way because "she knows her business better than we do." Long before the Rothmans, such philosophers were putting us on notice.