THE RIGHT TRACK

by Lewis Thomas

A friend of mine, a biomedical scientist with responsibilities for the future of one of the country's major research institutions, sent me a memorandum recently containing a set of questions about the application of biological science to medical problems.

Heading the list was the hardest and the most embarrassing: What are some examples, he asked, of the *usefulness* of the biological revolution itself, beginning with the discovery of the double-helical structure of DNA in 1953 and culminating in today's insights into gene structure and function, recombinant DNA, jumping genes, and all?

Must we assume, he asked, that medicine will always lag a half-century behind the rest of biological science, only capable of making useful applications when the last, final details of disease mechanisms have been revealed?

How can this process be speeded up, or *can* it be speeded up?

Questions like these are being raised more often today than ever before, in the press and in Congress—partly out of sheer impatience with what is perceived to be the slow pace of medical advance in treating or preventing today's major health problems; partly because medicine, in its present condition of incomplete half-way technology, costs so much more each year. And, partly because the justification for the spectacular national investment in basic research out of taxpayers' money during the past three decades has been the implicit promise that health problems can ultimately, and only, be solved in this way.

But here we are, 30 years down the line, and cancer, heart disease, stroke, and schizophrenia are still with us. Arthritis and multiple sclerosis have not disappeared. And more of us in our declining years are being incapacitated, and our families ruined, by dementia, or senility.

Could it be that we're on the wrong track, that science is the wrong way to go, that diseases like cancer and senile dementia are part of the human condition, that we should be doing something else?

Questions like these are being asked, and I have never known a time of such quick and ready answers. We become ill, it is now said, because of the environment we've created for ourselves, or because of failures in our life style, or because of lack of exercise, or being out of touch with our bodies, or, and this is the most fashionable of all, *thinking* wrong.

There is a serious question here underlying all the others and penetrating the noise: How can it be that we have learned so much in such rich detail about the inner workings of all sorts of cells and still be stuck with the unfathomability, for example, of cancer?

A Perceptible Buzz

Part of the uproar stems from the very fact that real scientific progress has been made with real medical applications of great value to society. Whenever this has happened, we quickly become used to the fact, taking such progress for granted as though it had always been there as a fixture in the culture. And we expect more to follow on. You don't have to look back more than 50 years to see almost the whole process.

Consider my father's experience. He was a family doctor in New York City with his office in the house for about half his professional life. Then he taught himself surgery and became a surgeon, which was the custom then. He was graduated from the College of Physicians and Surgeons in 1904 and interned at Roosevelt Hospital in Manhattan. He and my mother, who had been a nurse at Roosevelt, decided to move to a country town. They chose Flushing, now in the borough of Queens.

My father worked very hard all his life, but hardest during the years when he was a general practitioner. The telephone rang alongside his bed, and most nights we could hear him heaving himself out of bed two or three times, swearing softly to himself in the dark, and off in the automobile of the time, a Maxwell first and then later a Franklin, making house calls.

He told me once, during the 1930s, when I was still a medical student, that he couldn't convince himself that anything he

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Museum of the City of New York.

New York's Bellevue Hospital, 1860. Hospital doctors, wrote Oliver Wendell Holmes, carried infection "from bed to bed, as rat-killers carry their poison from one household to another."

had ever done for a sick patient during all those years of hard work had made any difference at all. The patients thought so, to be sure. My father was a successful physician with a large number of devoted patients who believed that he had helped them greatly, even saved their lives. But he was doubtful about this.

In his doctor's bag that he carried off in the night on house calls was a handful of things. Morphine was the most important, and the only really indispensable drug in the whole pharmacopoeia. Digitalis—for heart patients—was next in value. Insulin had arrived by the time he had been practicing for about 20 years, and he had it in his bag. Adrenalin was there in small glass ampoules in case he ran into a case of anaphylactic shock, which he never did.

But most of the patients who called him out at night could not be helped by the contents of that bag. There was nothing at all to do for someone stricken by acute rheumatic fever, or poliomyelitis, or meningitis, or tuberculosis. Least of all tuberculosis, which was the single disease most feared by my father and by everyone else in town. Once it had been typhoid that killed most people. Now it was TB.

The other disease that frightened everyone and was never talked about was insanity, but not today's version. What filled the state hospitals with demented people at that time was tertiary syphilis.

The pharmacopoeia at my father's disposal was enormous, and like all the doctors of his day, he wrote prescriptions of great complexity in Latin for almost all his patients. Most sought after by patients were "tonics." These were generally alcohol extracts of something green believed to act by toning up the heart and the muscles, or the liver, or whatever, and they were charms, magical potions sometimes reinforced by just enough alcohol to produce a perceptible buzz.

In effect, the pills were amulets warding off evil, and the prescriptions were incantations. If my father could have done a little dance at the bedside with his eyes rolled back, he would have qualified as a shaman in the ancient Indian tradition.

But he, and most of his colleagues in those decades from 1905 to 1935, did other hard things that had to be done to qualify as a good doctor. Medicines were only the ritual laid on as a kind of background music for the real work of the 16-hour day.

First of all, the physician was expected to walk in and take over. And second, and this was probably the most important of his duties, he had to explain what had happened and, third, what was likely to happen.

A Gift of Tongues

All three duties required experience to be done well. The first two needed a mixture of intense curiosity about people in general and an inborn capacity for affection, hard to come by but indispensable for a good doctor. And the last, the art of prediction, needed education. Good medical schools produced doctors who could make an accurate diagnosis and knew enough of the details of the natural history of disease to be able to make a reliable prognosis.

This was all there was to science in medicine. Indeed, the store of information that made diagnosis and prognosis possible for my father's generation was something quite new during the first quarter of the 20th century.

When he was an intern in 1905, the chief of the service on the medical ward at Roosevelt Hospital was an elderly eminence of New York medicine who was typical of the generation trained before the influence of Sir William Osler, who introduced skepticism into medical education.

This man enjoyed the reputation of a skilled diagnostician with a special skill in diagnosing typhoid fever, then the commonest disease on the wards of New York City's hospitals. He specialized in the tongue, not only placing reliance on the appearance of the tongue (which was then universal and is now entirely inexplicable), but he also believed that he could detect significant differences by palpating that organ.

The hospital rounds conducted by this man were essentially tongue rounds. Each patient would stick out his tongue while the eminence felt its texture and irregularities, moving from bed to bed, diagnosing typhoid in its earliest stages over and over again, and turning out a week or so later to be right to everyone's amazement. He was, of course, in the most literal sense a typhoid carrier.

The Dread Bacillus

When the time of psychosomatic disease arrived, my father remained a skeptic. He indulged my mother by endorsing her administration of cod-liver oil to the whole family, excepting himself, and even allowed her to give us something for our nerves called Eskay's Neurophosphates, which arrived as free samples from one of the pharmaceutical houses.

But he never convinced himself about the value of medicine.

In my own clinical years and in the wards at the Massachusetts General, the Peter Bent Brigham, and the Boston City hospitals, students were taught by Harvard's most expert clinicians, but all of the teaching was directed at the recognition and identification of disease. Therapy was an afterthought, if it was mentioned at all. Diagnosis was based almost entirely on the taking of a history, and a meticulous physical examination was the central business of the physician.

The transformation of medicine to something like a science with its own genuine technology was almost ready to begin, but it had not yet happened.

Mind you, this was in 1937, just a little over 40 years ago, on the eve of World War II. At that time, the thing to worry about the most was catching something. Infectious diseases were all around. There was a huge separate building alongside the Boston City Hospital called the South Department containing several hundred beds for contagious disease.

In the wards of the main hospital, lobar pneumonia was the chief problem. The work-up of a patient was an acute emergency requiring concentrated frenetic work for several hours on each case for the serological typing of the responsible pneumoccocci and then, if we dared do it, the intravenous injection of anti-

LOOKING UNDER ROCKS

In recent U.S. history, dramatic campaigns have been launched against two major diseases, polio and cancer. Both benefitted from political support—of very different kinds.

Poliomyelitis was classified as a distinct disease during the 19th century. After 1900, epidemics broke out annually in some part of the United States; the disease was at its worst between 1942 and 1953. While the existence of a polio virus had been pinned down in 1908 by Karl Landsteiner and Erwin Popper, further research lagged until 1938. In that year, President Franklin Roosevelt, a victim of the disease, launched the March of Dimes campaign and lent the prestige of his office to the fight against polio.

The new polio fund directors made a key decision: to spend money *not* on applying existing knowledge to the treatment of the disease (or "better iron lungs"), as had been the practice, but on basic research investigating the nature of the illness.

Between 1938 and 1955, the privately run March of Dimes dispensed $25.5 million to vaccine researchers; slightly more than $4 million was directly controlled by Dr. Jonas Salk of the University of Pittsburgh. Following refinements in research techniques and the definition of the disease, Salk announced discovery of a vaccine; a 1954 field trial proved it effective. The few polio cases that occur today (9 in 1978 versus 18,000 in 1954) are generally unfortunate side effects of innoculation with the vaccine.

Politicians have been declaring war against cancer since 1898, when the New York State legislature founded the Roswell Park Memorial Institute to find a quick cure for the disease. In 1910, President William Howard Taft budgeted $50,000 in federal money for the study of cancer in fish. Finally, in 1937, after a push from Henry Luce's *Fortune*, *Time*, and *Life* magazines, Congress estab-

pneumoccocal serum, a chancy and hazardous but sometimes brilliantly successful treatment.

For all the others, the streptococcal infections, epidemic meningitis, staphylococcal septicemias, endocarditis, whooping cough, polio, and all the rest, there was absolutely nothing to be done beyond providing good nursing care and hoping for the best.

And the disease to worry about the most was tuberculosis. It was all around. Anyone could catch it at any time from infancy to old age. Rest was the only marginally useful treatment: rest for the whole body in bed, and technologically-induced rest for lished the U.S. National Cancer Institute (NCI). But cancer researchers have never had an FDR as patron, and there has been no consensus on how to spend the money appropriated by Congress.

Cancer became embroiled in Washington politics in the early 1970s, when, against the advice of most American scientists, Congress voted for a "moon-shot" type of crash program to find a cure. (Researchers like Harvard Medical School's Dr. Howard Hiatt resisted the spending spree, warning that the necessary "science base" had not yet been established.) The annual budget of the National Cancer Institute is now nearly $1 billion, versus $175 million in 1970. In the period from fiscal 1972 through 1981, NCI spending will total $7 to 8 billion—three times the total federal cancer outlay from 1938 through 1971. Almost one-third of NCI's current spending is on "unfocused" basic research—simply finding out "more about the universe," in the words of National Institutes of Health director Donald Fredrickson.

Some good work is being done. But despite modest gains, researchers are still groping blindly; conceivably, just about any scientific investigation now being carried on in America could turn out, in retrospect, to have been work on cancer. There is a "looking-under-rocks" aspect to cancer research. After polio was discovered to be a virus, finding a cure became only a matter of time. In cancer research, on the other hand, scientists are still looking for what to look for.

March of Dimes Birth Defects Foundation.

The first polio poster child.

the affected tissue by injecting air into the pleural space to collapse the lung temporarily, or cutting away the ribs to collapse it permanently. There were no drugs of any value at all.

The basic research on tuberculosis was begun in the 1890s with Robert Koch in Germany, and the effort that followed the discovery of the bacillus over the next 40 years consumed the scientific lives of hundreds of investigators in laboratories all around the world. Gradually, they gained a fairly clear understanding of the ways in which tuberculosis became disseminated throughout communities, and the public health techniques for early detection and isolation were developed. The underlying mechanisms enabling the tubercle bacillus to destroy living tissue were explored (although the matter remains to this day largely a mystery), and some of the factors in the environment that affected the course of the disease were identified: crowding, malnutrition, genetic predisposition perhaps, immune responsiveness, and possibly even the stress of living.

The whole mass of results of research on tuberculosis filled numberless huge volumes in the world's medical libraries, but throughout 40 years the central, absolutely crucial piece of fundamental science was the information that the tubercle bacillus was the real cause of the disease and the sole cause.

Faith Healing

Other factors, environmental or genetic, might be contributing to susceptibility or making a difference for the final outcome, but at the center of the theoretical demonology was that bacillus; there was no argument about this. If you could get rid of the tubercle bacillus and kill it off without killing the patient, you could cure the illness.

This was the scientific background that led to the work of Nobel Prize–winning microbiologist Selman Waksman with his inspired hunch that some of the microorganisms living in the ecosystems of the soil might produce chemicals capable of restraining the growth of other competing bacteria.

But without the existence of the tubercle bacillus in hand, there would have been no point in looking for something with the properties of streptomycin, nor any technique for screening samples of soil for anti-tuberculous activity.

Streptomycin, developed by Waksman, was an immense encouragement, but it was not good enough. It helped, but it actually cured only those patients with relatively early disease. It could not be relied upon to reverse the devastations of miliary tuberculosis or TB meningitis.

Nevertheless, it was a gift of hope, and it proved that tubercle bacillus was vulnerable in living tissues. Given this hope, the investigators set about looking for other drugs to enhance the action of streptomycin, and para-aminosalicylic acid was found. Then a few years later came isoniazid, and the conquest of tuberculosis became at last a stunning success.

However, scientists argue about this point today. Looking back at the records of infectious disease in Western society over the past two centuries, it is obvious that the incidence of most bacterial diseases began to fall long before the introduction of the sulfonamides and the antibiotics.

A DRIFT TOWARD CAUTION?

There is a tendency now throughout the whole federal science system favoring the taking on of relatively safe and sound research projects. There is a general disinclination to gamble, to take fliers, to run risks on flights of imagination. Running risks is considered to be simply too risky.

This drift toward caution and this new concern for getting tidy things done on schedule could be the deadest of dead hands on science, and I am fearful of it.

I realize that it is the result, perhaps the inevitable result, of the shortage of funds in a highly competitive system, but this is not the whole cause. I have a feeling that fundamental attitudes within the bureaucracies responsible for science have also changed, and there is more and more an insistence that research must be planned and performed like any other job of work, contracted for and paid for by public money.

Perhaps this was inevitable once the national science support programs became of such sheer magnitude as to hold them under constant public scrutiny. Who can go about in a bureaucracy calling for more chance-taking, more gambling, and hope to survive? And yet, the stakes here are very high indeed. It is not just basic research in the biomedical sciences that is at issue; it is basic science in general.

We cannot go on drawing down from the banked store of fundamental information about nature without constantly replenishing that bank; if we do this we will find the country drifting further and further behind the rest of the world.

—L.T.

The mortality from tuberculosis was being halved every 20 years since the mid-19th century, and something like this was also happening to pneumonia and streptococcal infections.

This steady improvement in human health has been variously attributed to better sanitation, better nutrition, better housing, less crowding, and a generally better standard of living for all segments of society in the West.

Looking at these events, a number of influential epidemiologists and public health professionals have suggested that perhaps the impact of chemotherapy on infection was an illusion. We would have gotten where we are today relatively free from the threat of tuberculosis and the other infectious diseases without scientific medicine, it is said, by allowing society to continue to improve our ways of living together. Fix society, fix the environment, change our lifestyles, mend our ways—and human disease will vanish.

If you believe this, you automatically take a different and highly skeptical view not only of the social value of medical science in the past but also of its prospects for the future. You can get along by abstinence and jogging and maybe a bit of faith healing. It has an undeniable appeal.

My own view of the argument is a totally biased one, but I cannot help this. I have been conditioned by the experience of seeing children with miliary tuberculosis and tuberculous meningitis cured of their illnesses that were by definition 100 percent fatal in my student days, and I saw no reason to doubt my eyes.

I have watched patients with typhoid fever and meningitis and streptococcal septicemia and erysipelas and overwhelming pneumococcal infections get better, sometimes overnight, and I am as certain as I am of my sanity that these were real events and not illusions.

In short, I haven't any doubt at all as to the effectiveness of today's antibacterial and immunological measures for disease control, although I am worried about the future of antibiotics (as is everyone else in the field of infectious disease) if we do not continue to do research on the appalling problems of antibiotic resistance among our most common pathogens.

Small Steps

As we look back at a cure for tuberculosis, I think we are today perhaps somewhere along in the same sequence of scientific events for cancer. The ambiguous word *somewhere* is needed here because we do not yet possess pieces of information with anything like the power of Koch's identification of the tubercle bacillus.

We know a fair amount about environmental influences including the irrefutably convincing evidence about cigarettes and lung cancer, but we do not yet know what happens at the center of things to switch normal cells into the unrestrained life of neoplastic cells.

However, we do seem to be getting there. At least I think so. It is unlikely that a virus or some kind of infectious agent is involved, but there is in any case a high probability that a centrally placed regulatory mechanism whose nature remains to be elucidated has gone wrong and that it is the same mechanism for all forms of cancer.

The most solid evidence of scientific progress has come just in the past five years or so. The drugs now in use are not nearly as debilitating as those available a decade ago. A great deal has been learned about the value of intermittent therapy with combinations of several drugs, as well as about the value of combining chemotherapy with radiation treatment.

There have been advances in the complicated technology of radiation itself to the extent that Hodgkin's disease, which was a totally untreatable condition a generation ago, is now generally accepted to be curable.

The malignancies of childhood, including bone sarcomas, are beginning to respond so well to chemotherapy that it is becoming permissible to talk, tentatively at least, about cures.

Cures Are Possible

In short, some real advances have been made and are being made today in the treatment of cancer. All around the world, research at the basic science level has been turning up new bits of information in the fields of molecular genetics, immunology, cellular biology, membrane structure, and the like; and although nobody would claim that we have as yet an understanding of the underlying process of neoplasia, it is generally agreed that the problem is an approachable one. It is a puzzle that can eventually be solved.

There was a time less than 50 years ago when no one in medicine would have dreamed of the possibility of ever curing subacute bacterial endocarditis. This was one of the master diseases, 100 percent fatal, and we stood in awe of its power to kill people. Hence medical students were taught not to meddle. There was nothing to be done, and never would be. There was a time when most professionals dealing with poliomyelitis were totally pessimistic about the prospects for anything other than iron lungs in this disease. Generations of physicians were trained to believe that tuberculosis was an undefeatable enemy of mankind.

It is really only within the last 40 years or so that most of us have become convinced that it is possible to cure certain human diseases, and even now there are some major disorders for which our minds are set against the possibility.

We tend to be deferential about chronic illnesses simply because they are chronic, as though there were something especially imponderable about a disease that occurs late in life and lasts a long time. In the absence of good sharp clues about etiology or pathogenesis, we tend to use terms like *multifactorial* or *environmental.* We talk about certain illnesses as being *societal* in origin. And we do this for most of today's diseases that are not yet understood: coronary thrombosis, stroke, atherosclerosis, schizophrenia, arthritis, and, most of all, cancer. They are often discussed as though they were part of the human condition inevitable in our kind of world and beyond our reach.

And it may be that this attitude gets in the way of research from time to time.

Yet the professional investigators who are actually working on the mechanisms of our still unexplained diseases seem more optimistic about the prospects for their respective fields than at any time previously. It is interesting that each of them is skeptical about the chances of the others. The immunological people feel that they are beginning to work quite close to the center of things, but they doubt that their colleagues in neurobiology or cardiology are getting anywhere, and so it goes. The virologists and molecular geneticists and cell biologists each believe that they will have the crucial answers before anyone else.

The overall atmosphere is, however, one of considerable excitement and anticipation. There are groups of young researchers in laboratories located in New York, Dallas, Pasadena, and Paris who are working together with colleagues in Melbourne, London, and Tokyo almost as intimately as though they were in the same corridor of the same building.

So I am entirely optimistic about the prospects for biological and medical science for the future, the long-term future.

I believe that immense advances have been made in just the last 30 years in our understanding of how normal cells work, how tissues develop and become organized, how cells communicate with each other by chemical signals, how organisms defend themselves, and even, in glimpses, how the brain works.

I do not believe there are any barriers to prevent our reaching a deep understanding of disease processes, and I see no reason why we should not be able ultimately to gain a reasonably satisfactory control over human disease in general.

This has nothing to do, by the way, with mortality. We will still die on schedule and probably on something pretty much like today's schedule, but I think we can spare ourselves the incapacitating and painful ailments that now make aging itself a sort of disease.