ABSTRACT

The concept of analytical and diagnostic "metabolomics" originated as "metabolic profiling" in the 1970s. Largely ignored by the $100 billion commercial clinical laboratory industry and the medical monopoly that it serves, this discipline can now be brought to fruition, as a result of miniaturization of analytical devices, advances in personal computer technology, and development of the Internet. With these tools, metabolic profiling, as well as on-person monitoring, medical imaging, and other powerful diagnostic tools, can be placed in the hands of consumers, who will then be able to control the quality of the information and medical care that they receive. Medicine can be turned into a therapeutic industry competing solely on the basis of quality and price. The gatekeepers of medicine can be bypassed, preventive medicine can grow, early detection of illnesses can greatly expand, and sophisticated yet inexpensive monitoring of response to medical interventions can markedly improve therapeutic medicine. These advances can greatly diminish human suffering and provide substantial improvements in human health and longevity. Moreover, with these improvements, economic costs in the medical industry can be sharply reduced, freeing hundreds of billions of dollars in capital annually to be used for other improvements in human life.

Licensure laws, governmental regulations, and a vast interlocking system of institutionalized restrictions have created an impenetrable monopoly that now stands between medical consumers and physicians and medical facilities. This is the most powerful and highly paid monopoly in human history—now demanding 17 percent of the entire annual gross domestic product of the United States in return for its services. Not only the supply of goods and services but also the evaluation of medical products and services is under monopolistic control—by physicians and institutions and increasingly by insurers and governmental and quasi-governmental agencies. American medicine is an unusual monopoly because it controls not only the supply of its products but also the evaluation of its products by consumers, and it inhibits independent consumer evaluation of its work.

If my son Matthew takes his dog Rusty (Figure 1) to the veterinarian, the veterinarian can measure, within a few minutes, a couple dozen substances in a blood sample from Rusty—the same substances that will be measured if you go to a physician and his nurse takes an ordinary sample of your blood. The veterinarian does this with a personal computer peripheral costing about $1,000. Some veterinarians instead send animal blood samples to local hospitals, where they are analyzed by the medical devices used for human specimens. The veterinarian cannot, however, use his device to analyze a sample from Matthew. This is unlawful. It would also be unlawful for a physician to measure Matthew’s sample, without government approval of the device and certification of the doctor’s lab under the Clinical Laboratory Improvement Act—a bureaucratic requirement that is beyond the means of most physicians. The federal government tightly controls the facilities and personnel allowed to make diagnostic measurements on human specimens. Most measurements are done in commercial clinical laboratories, and most of those laboratories would refuse to measure a sample if Matthew asked them to do so. They would require a physician’s order. There is, however, a solution to this repressive situation. Matthew can measure his own sample. If he does it himself, it is lawful.

Historically, medicine had very little technology, and medical knowledge resided primarily in the minds of physicians. As medical technology developed, especially diagnostic technology, expensive machinery was required. The early analytical machinery and computers were very expensive and required an elaborate infrastructure to use and maintain. A $100 billion industry has evolved around medical diagnostic information, including that obtainable from samples of human blood and urine. As the medical monopoly has matured, the commercial laboratories have been sequestered behind the gatekeepers of medicine. Individuals cannot utilize this diagnostic technology themselves. Moreover, advances are delayed because the medical monopoly is slow to change, so diagnostic methods have fallen far behind the general technological advance.

In fact, the diagnostic techniques offered by veterinary analytical laboratories to Rusty’s veterinarian are often better than those offered by human diagnostic laboratories to Matthew’s doctor. When a new technique is discovered, veterinary laboratories are permitted to immediately provide it to veterinarians. Approval by the medical monopoly of the technique for human use, however, requires enormous amounts of time and...
money. This not only results in delays and raises the ultimate price of the diagnostic technique, but also causes many useful procedures never to be available to humans at all.

Quantitative Measurement of Human Health Is Required

In order to make significant progress in preventive, diagnostic, and therapeutic medicine, it is necessary to have methods for the quantitative measurement of human health. Consider just the simple question of determining the optimum amount of an essential nutrient in the human diet, as illustrated in Figure 2.

It would be useful to have this curve for each essential nutrient ingested by an individual, but this requires a convenient method for measuring the quantities on both axes, including the quantitative measurement of health. A similar situation exists for nonessential but useful variables except that health is above zero when the intake is zero. This includes therapeutic drugs and also other changeable parameters such as the amount of exercise.

Moreover, biological, environmental, aspirational, and health variability between different individuals as illustrated in Figure 3 requires that these curves be constructed for each individual human.

The population curves in Figure 3 also cannot be constructed without a rigorous means of measuring health quantitatively.

Preventive medicine requires quantitative methods. Figures 2 and 3 illustrate this. In order for health to be optimized, it is useful to know the optimum intake of each nutrient. Figure 2 illustrates a curve for an essential nutrient such as a vitamin or essential amino acid. There is no health without the nutrient. As intake rises, health increases to a maximum and then decreases. In order to determine the intake for optimum health, it is necessary to measure health quantitatively, easily, and frequently. Also, since biological variation, as illustrated in Figure 3, causes the optimum values to vary between individuals and within the same individual as a function of age, health, and other circumstances, inexpensive and easily available frequent quantitative measurements must be available to each person.

Lack of quantitative health information leads to premature suffering and death, as illustrated by the lifespan curve for men in the United States in 1974 shown in Figure 4. This curve has not substantially changed in the past 30 years even though technological advance in most other areas has been extraordinary. At tragically early ages, in their 30s and 40s, people die. Moreover,
there is great suffering associated with this process. This is not a good life-span curve. A research scientist would prefer not to use an experimental system that exhibited this curve for intrinsic longevity experiments.

The aging curve for well-cared-for fruit flies has a rectilinear shape, like the upper curve shown in Figure 5. The curves for mice and other animals are similar. Well-cared-for animals have a good chance to live out most of their full intrinsic life spans and then to die over a fairly short span of ages. Fruit flies are cold-blooded, so the life span can be changed by varying the temperature, but the shape of the curve remains rectilinear, with few deaths during early life. The human lifespan should have a rectilinear curve like the upper line in Figure 5. If the curve is rounded as in the lower line in Figure 5, something besides intrinsic aging is taking place. Unfortunately, this lower line is the curve today for people in the United States.

The lower curve in Figure 5 also illustrates one of the reasons medical care is so expensive. Medical intervention is often needed throughout the lifespan instead of just between the ages of 80 and 100.

Squaring the human curve as shown in Figure 5 and thereby giving every human being a full life of good health throughout his intrinsic human life span should be the first goal of medicine.

Surely our medical system, in this age of high technology, should be able to give human beings an opportunity for the same life span curve available to laboratory fruit flies and mice.

A second medical goal should be to extend the lifespan curve—to increase the intrinsic human life span as is illustrated in Figure 6. We know from experiments on animals—especially experiments with diet restriction, which decreases the age-specific mortality at each physiological age, and mild temperature reduction, which decreases the rate of physiological aging—that about a 30 percent extension can be achieved in most of the many animal systems that have been studied. This is probably also possible for man.

A third goal is futuristic, as illustrated in Figure 7. When science eventually understands the molecular clock for aging, and if that clock is susceptible to adjustment, we may be able to live a very long time. This is not a concern of current ordinary medicine.

The most important impediment to making progress in improving the human life span curve as illustrated in Figure 5 is the lack of methods for the quantitative measurement of health. Many interventions to improve longevity have been suggested, but few have been experimentally verified for individuals. If, however, we had a method for quantitative determination of physiological age, we could make frequent measurements and determine whether taking vitamin E, exercising, eating vegetables, and so on, had a favorable or unfavorable effect on our own personal age-specific mortality. Each person should be able to determine his physiological age quantitatively, so that he can adjust his circumstances to minimize his own personal rate of aging. This is illustrated in the first bar of Figure 8.

People should also be free to fight the probability of disease rather than disease itself. This is illustrated by the second bar in Figure 8. They need low-cost, frequent, quantitative measurements of the probability of illness for themselves individually in order to accomplish this. Epidemiologic and correlational studies for entire populations as appear often in the press are of very minimal use to individual people. Moreover, genetic predisposition studies are also of little value. The individual cannot change his genes, but, if
Finally, in order to improve human health, the people involved must comply with the health measures that are indicated. This compliance is often difficult to obtain. We already know, for example, that cigarette smoking is harmful to the health of many people and often leads to a shortened life. Still, people smoke cigarettes. Similarly, even people who are seriously ill with treatable diseases often do not follow a useful therapy properly. The ability to measure the effects of a change in habits or of a therapy provides a strong incentive for compliance. A dieting person can easily monitor his weight with an ordinary scale, so he can observe his progress and is more likely to continue with dietary restraint. The ability to easily and frequently measure one’s health quantitatively raises the probability of compliance with health measures because improvements or deteriorations as a result of one’s own actions can be easily observed.

In the case of serious disease, frequent quantitative data is especially useful to both the patient and the doctor. If a cancer therapy leads to a slowing of cancer growth, then there is a strong incentive to continue. If, conversely, cancer growth remains the same or accelerates, a change in therapy is indicated. This information needs to be inexpensively and quickly available with as many longitudinal data points per patient as possible, especially in the case of a life-threatening illness. Patient-based diagnostics can fill this need, which, in the hands of the current medical monopoly, is largely neglected.

Moreover, quantitative measurements of individual health can markedly accelerate therapeutic medical research. More than a decade ago, it was reported that certain dietary changes reduce the growth rate of squamous cell carcinoma in mice by ten-fold, while other dietary changes increase that growth rate by two-fold. This is a variation in growth rate of cancer by 20-fold as a result of dietary change alone. Yet, there has been no action on this discovery among the so-called normal ranges. If—a single parameter is more than two standard deviations from the normal and therefore in the top or bottom 3rd percentile, the physicians look in the textbooks or their memories and conclude that this must have a certain meaning. Even in the standard set of about 20 blood parameters, much of the potential information is, therefore, ignored.

If one did nothing more than classify each parameter as above or below the mean and consider profiles, there would be 2^20 or more than 1 million different patterns. Quantitative data on the distances above and below the means gives even more variants and concomitantly more information. These variants and their implications cannot be manipulated in a human brain, even that of a very skilled physician. Long ago, clinical laboratories should have been interpreting blood profiles and other analytical data by computerized pattern recognition techniques and providing these interpretations to the physicians. The fact that they still do not do so is a sad commentary on the quality of current monopoly-driven medicine.

The measurement of only 20 parameters requiring an expensive and time-consuming visit to a physician’s office in the age of the Telecosm is a hopelessly antiquated procedure. A wealth of valuable information can be derived from profiling the quantitative patterns of small molecules in human urine, blood, breath and saliva. But this is not done.

In the 1970s, when I suggested this data evaluation to the executive in charge of one of America’s largest clinical laboratory companies, he replied, “Why should we do this? We are making good money doing what we are doing.” He might have added that taking the lead in changing any procedure in the vast medical-industrial-governmental-litigational monopolistic complex is a daunting, thankless, expensive, and often dangerous undertaking.

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In the 1970s, my coworkers and I set out to do this. Being young and naïve, I thought, “All we have to do is develop improved procedures for medicine, and we will improve people’s lives.” With my coworkers, including Linus Pauling, I invented a new discipline that we called “metabolic profiling.” It is now called “metabolomics.” This work involved the extraction of information from the normal metabolites that are found in urine, breath, blood, and saliva and discovering the profiles that are associated with various clinical states. We built the most sophisticated computerized chromatography and mass-spectrometry laboratory of that era and quantitatively measured, in thousands of human body fluid samples, 50 or 100 or 200 parameters—as many could be measured by a particular technique. After verifying a useful pattern, we reduced this information by appropriate mathematics to quantities of linear decision axes, as illustrated in Figure 8.

We worked out all of the necessary analytical procedures and mathematics, published 20 research papers, and demonstrated that
we could see many useful patterns and could measure physiological age quantitatively. The machines we developed in the 1970s could sniff a urine sample from each person reading this paper and determine a profile that would be characteristic of each individual. If the same people were measured next year, each sample could be reliably paired with the first one, as each person is biologically unique. Moreover, individuals are unique at birth. In studies of 1,000 newborn infants, we showed that the urine metabolites are not unimodally distributed. They are bimodally and trimodally distributed in accordance with genetic characteristics.

This powerful new technology for the quantitative measurement of human health did not, however, improve human health. It was not adopted by the medical monopoly. The computers of that day were maintenance intensive and expensive, as was the analytical apparatus. So, application would have required analyses in a commercial medical laboratory, and none were interested. They were making good money doing what they were doing—and they are still doing so.

**Metabolites Are Especially Useful**

The Human Genome Project has caused much excitement, and there is great interest in sequencing DNA. This can be useful. However, if there is a leak in the roof of your house, the immediate solution is not likely to be found in the design drawings of your house. Moreover, practical techniques that modulate the genetic information in a living human being for ordinary purposes are many years in the future.

There is information in a person’s DNA, and in his proteins, and in sophisticated images of his body. But the greatest amount of information is in his metabolites, the small molecules that are produced and consumed in the normal course of metabolism. These molecules are the immediate result of most biochemical activity. Moreover, they are interlocked in many different biochemical pathways. Therefore, it is not necessary to measure every one. There may be 5,000 substances of importance, but a sample of 500 carries information about the other 4,500 as well. For example, about 30 percent of the substances in urine are correlated with physiological age. Some go up with age. Some go down with age. It is not necessary to measure 5,000 compounds. A subset of 200 is sufficient to reliably measure physiologic age.

In the 1970s, in our laboratories at the University of California at San Diego, Stanford University, and later at the Linus Pauling Institute, we built high-resolution chromatographs, and we also built the first molecular-ion mass spectrometers for our metabolic profiling project. Figure 9 shows a 1970s computerized urine vapor and breath analyzer that we constructed and a sample urine vapor chromatogram measured with this instrument. The chromatograph was used to “smell” urine or breath. We then carried out mathematical pattern analysis on the measured amounts of the components.

Figure 10 shows the ultimate use that we had in mind. I put Linus on the ladder with vitamin C in his pocket and sugar in the waste basket, reflecting some of our other interests.

In those days computer work was difficult. We had the first PDP-11 computers at Stanford. Figure 11 shows our systems programmer,
Laurelee Robinson, my wife and the mother of our six children, at work. The storage media, DEC tapes, had a capacity of 256 kilobytes. We were very pleased when we received one of the first RK02 disk memory units, which had a capacity of one megabyte.

Figures 9 to 11 also illustrate why these new techniques did so little to advance human health. Since they required expensive analyzers and computers, they could only be introduced through the clinical laboratory system, and the medical monopoly is not interested in change. Even today, in our laboratory at the Oregon Institute of Science and Medicine, we work with a commercial molecular-ion mass spectrometer that costs more than $1 million and weighs 3 tons. Despite its wonderful capabilities, it too will probably not realize its potential to help human beings under the current monopolistic medical system because such equipment always winds up behind the gatekeepers.

**Revolutionizing Medicine with Personal Analytical Devices, Personal Computers, and the Internet**

Now, however, technological advance has made possible the practical quantitative measurement of human health by medical consumers themselves and the dissolution of the medical monopoly that has impeded progress.22

Chromatography and electrophoresis, separation techniques useful for metabolic profiling, are being performed by chip-based devices. Mass spectrometers that you can hold in your hand are being developed. Technology has advanced to the point that these analytical devices can now be packaged like laser printers and installed as peripherals for home computers. While we could measure about 200 parameters with our elaborate equipment in the 1970s, I estimate that it is possible to measure about 300 today, in urine, breath, saliva, or blood, with analytical devices that could sit on a desk top, be mass produced, and sold in office supply stores and by other similar retailers.

Moreover, measurements that are inexpensive and under the control of the consumer can be done very frequently, producing longitudinal data for each individual. This removes biochemical individuality between individuals from the data interpretation and markedly increases the extractable useful information content of the analyses. Each individual can compare his current status with his own status in the past, rather than with that of an entire human population.

At the Palo Verde Nuclear Generating Station near Phoenix, Arizona, three steam generators, powered by three modest nuclear reactors, continuously produce 4 gigawatts—sufficient electrical energy for the ordinary needs of more than 3 million homes—by means of the safest, least expensive, most environmentally benign technology now available to man. These generators have enormous drive shafts rotating in very large bearings. Usually, engineer operators of machines with such drive shafts do not wait for the bearings to squeak and then put them on a treadmill for a stress test to determine what is wrong with them. They instead embed small vibration sensors in the casings and develop a longitudinal computerized record of the individual vibrational “personality” of each bearing. If that personality changes, the bearing is immediately examined.

Analogous methodology can help human beings today. Consider, for example, heartbeat. With a wrist monitor and transponder that downloads into a personal computer, a complete record could be obtained of every beat of a person’s heart over many years—under all sorts of conditions: excited, calm, awake, asleep, well, sick, with strenuous exertion, at rest, fasting, after eating, and so on. A change in pattern would provide an early warning of problems. Every person should wear a device of this sort, including all infants.

For biochemical profiling, analysis of breath may have the greatest potential. A breath-analyzing peripheral attached to an individual’s personal computer could simply analyze his breath while he works at the computer. This is not science fiction. It has recently been suggested that breath monitors be placed in public restrooms to detect increases in infectious diseases that could arise from bioterrorism.

Moreover, great increases in the quality of medical data analysis are available. Once consumer-based analyzers—including one-person analyzers, computer peripherals for physiological measurements, and other similar technologies—are being built and distributed, a competitive, Internet-based industry can arise for interpretation. A consumer could potentially access all of the people in the entire world who understand software and mathematics and the relevant medical information, rather than being restricted to a relatively inaccessible and expensive doctor whose expertise is unlikely to be the best available.

Some technologies are inherently too costly to place in the hands of the consumer. Advanced MRI and other imaging machines are currently too expensive for home use. However, they can be placed in shopping centers. With mass production and high-volume use, the cost of making the images would be lowered dramatically. The consumer—stopping for a few minutes during a shopping trip to a local mall—could receive his own MRI image data on a CD for perhaps $50 per scan and later send it from his home personal computer to the Internet company of his choice for interpretation. Even high-cost imaging technology need not remain behind a gatekeeper.

Figure 11 shows Laurelee Robinson at work. During her many years of work in this field, Laurelee became the first metabolomics computer systems programmer in history. She contributed very substantially to the advance of this field. One day in 1988, however, Laurelee developed a stomach ache. Five of our six children—ages 1 to 12—also had tummy aches. She had consulted physicians twice over the preceding several months for abdominal pain, and had been sent home both times with a laxative. These gatekeepers decided that she merely had a mild bowel obstruction.

When I asked her that night whether she wanted to go to the doctor she said, “No, let’s see how I feel in the morning.” You see it was late at night, the emergency room was an hour away, they would charge $1,000 and keep us for hours, and they might not find out anything anyway. The gatekeepers were a long, expensive, tiring distance away for a sick lady in the middle of the night.

Before morning, Laurelee did not need a doctor. She was dead. She died of hemorrhagic pancreatitis, which would have been detected by the most primitive urine profiling analyzer. She was the...
world’s foremost expert in acquisition and analysis of data of this kind. Her illness could have been detected by a blood sample sent to an ordinary clinical laboratory of that time, if the gatekeeper had happened to ask for a specific blood assay that is not otherwise performed. She could have been taken to surgery promptly. But instead she died, because diagnostic medicine was behind the gatekeepers of the medical monopoly.

Laurelee lost her life, but the gatekeepers lost nothing. For them, there is always an unending line of frightened and suffering people waiting patiently for their inconveniently scheduled, monopolistically priced, and outmoded services. The American people are so fearful of the medical monopoly that they spend a very large part of their disposable income for medical insurance—to increase the chances that the gatekeepers will see them if necessary.

Ending the Medical Monopoly with High-Technology 21st Century Medicine

Today, technological advances have made possible the production of consumer-based analytical devices for the quantitative measurement of human health. These include computer peripherals for the measurement of metabolic profiles in human breath, urine, and other body fluids, and on-person monitors for simple parameters such as heartbeat. Suitable computer technology for control of and data collection from these devices is already present in most American households. Moreover, for those technologies still too expensive for personal use and for people whose circumstances are not suited to personally controlled monitoring, facilities in public places such as shopping centers can offer access on a mass-delivered, inexpensive basis.

High technology now makes possible far more physiological data than is routinely available in medical institutions. Universal, inexpensive, frequent access to quantitative data about one’s own physiological health makes possible major advances in health and longevity. Personalized data, longitudinal data, and data independently obtained without filtration by a self-interested monopoly enables further substantial advances in the usefulness of this information.

Moreover, the Internet has created an environment in which data transfer throughout the world is essentially free. This provides the consumer with access to literally everyone on earth with talent and experience in the analysis of physiological and biomedical data. Free-market competition within the Internet can markedly increase the quality and usefulness of this data analysis.

This technological revolution can not only end the medical industry’s monopoly of the evaluation of its own products, but it can provide thousands of times more useful medical information to consumers than is presently offered by that monopoly.

When this technological revolution has run its course—and it will do so regardless of the institutional, governmental, and litigational impediments that the medical monopoly currently places in its way, medicine will be reduced to a service industry competing on the basis of quality and price, with consequently far higher quality and much lower prices. This will free hundreds of billions of dollars in American capital that is currently wasted annually in an antiquated medical system.

How long will this revolution be in progress? No one knows, but every day that is saved can be measured in human suffering and death that will not take place. American freedom—the freedom to act on behalf of one’s self—can cause this transition to take place very quickly. Each American has the freedom to measure and to communicate his own health information by means of personal computer technology and the Internet. This does not require governmental approval.

Matthew can be as free as his dog Rusty. He can act for himself, even though he is legally constrained from acting for others. Fortunately, the 20th and 21st century revolutions in analytical technology, computer technology, and communications technology have made it possible for engineers and technologists to provide Matthew with both the freedom and the power to act effectively on behalf of his own health. The sooner this is done, the more unnecessary suffering and death will be prevented.

Universal Use Matters

Some wealthy people will say that this revolution need not take place for them. They will consider it unnecessary to improve everyone’s health. They have plenty of money to buy the very best. Just tell them, they will say, where to order these new methods.

The fact is, however, that the new methods will not be available at all without a mass market to support them. The engineering, manufacturing, marketing, calibration, and interpretation required to make these new technologies useful requires a mass market.

A wealthy person is able to buy a personal computer because a mass market of ordinary people has made possible the capital-intensive industries that produce those computers. The same is true of 21st century medicine. If one wants the best medicine modern technology can provide, he should support the industries that can develop that technology for everyone—regardless of his personal humanitarian instincts.

Conclusion

Destruction of the medical diagnostic monopoly and its replacement by individual-based high technology must take place. When this finally occurs, it will: (1) make possible an extraordinary increase in the quality and length of human life; (2) cause a marked decrease in the amount of human suffering; and (3) free an immense amount of capital that is now being wasted in an obsolete and ineffective medical system.

Implementing this revolution constitutes a moral obligation of our current generations to the previous generations of scientists, engineers, and entrepreneurs who have made this possible, and to the hundreds of millions of human beings, including yourself and those you love, whose health and lives will be enhanced.

Arthur B. Robinson, Ph.D., is President and Research Professor of the Oregon Institute of Science and Medicine, 2251 Dick George Road, Cave Junction, OR 97523.
REFERENCES


