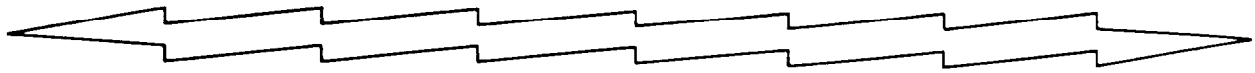

ELECTRICAL ENGINEERING: THE SECOND CENTURY BEGINS

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ELECTRICAL TECHNOLOGY AND THE MOLECULAR BIOLOGIST

Joshua Lederberg

My career is that of a molecular biologist. But when you visit my office, you will notice that my diploma as a member of the Institute of Radio Engineers is one of the very few that I keep on my wall. It recalls to me the very exciting time that I had working with Lloyd Berkner when he was Chairman of the National Academy of Sciences Space Science Board. He recruited me into the IRE in January 1961 when he was president of that organization, predecessor to the IEEE.

In fact, the first issue on my member's subscription was a special one on artificial intelligence. It included articles by John McCarthy and Marvin Minsky that were influential in drawing my own interest into that field. Why would a molecular biologist care about computers and, particularly, about artificial intelligence? I felt that we were reaching the limit of our intellectual capability of modeling the complexity of the living systems, the molecular biology that was just growing up. These are systems whose complexity is the fruit of four billion years of evolution under spontaneous mutation and natural selection, plus, and very importantly, every trick of molecular chemistry with which God had invested the earth from the beginning, and many of these we are far from understanding fully. So I joined with Ed Feigenbaum and Carl Djeressi, and I had fun *discovering* (rather than inventing) expert systems.

This meeting is a celebration of electricity, but this now also means software, as betokened by the Computer Society within the IEEE.

Twenty years ago, I did prognosticate; I was looking forward to what molecular biology might bring to our future, and I have to say, as I look over my writings, most of the things I talked about have come to pass. If I was in error in a few places, then some advances were even more rapid in their substantiation than I cared to dream about at that time. So it is not out of modesty about my box score in that prophetic mode that I decided not to pursue that mode tonight. Rather, in reflecting over my own career, I cannot see how those prophetic remarks, however correct or incorrect, have made any difference whatsoever. The things that were to come about have come about. If I have made any contribution to the present state of science, technology, or any other aspects of the world's condition, it has been entirely through my laboratory investigations, through the actual study of the nature of living organisms.

Thus I thought I might focus on that and on the ways in which there are, in our future, very strong intersections of my field and yours, which I have tried to internalize in my own interests. Fig. 1 is a flowchart that shows something of the complexity of intermediary metabolism. This is a crystallization of 50 years of biochemical investigation, which have revealed to us the larger number of the substances involved in the degradation of food stuffs into common small carbon constituents; their oxidation; the conversion of their chemical-free energy, usually into the common medium of adenosine triphosphate; and the use of that energy in a variety of metabolic cycles to fire up other biosynthetic mechanisms. If you walk into almost any biochemist lab, you will see the same chart; it will cover a whole side of a room, because each node will have the name and the molecular formula of a given substance on the chart. There are about 400 molecules of molecular weight averaging 150 or 200 that have been pretty thoroughly worked out, and they probably account for most of the simple building blocks of our bodies. However, these unit blocks, like the bits in a computer, are assembled into much more complex architectural constructs.

The flowchart shows the conversions that these compounds undergo: how glucose goes into small carbon fragments, and how those small carbon fragments can be built up again into amino acids, purines, and other growth factors. (Sometimes we must get these from synthetic activities of other organisms.) The chart shows nothing of the regulatory mechanisms, which must be very exquisitely controlled. It simply will not do if you produce twice as much tryptophan as you need for the manufacture of your own proteins, and have a deficiency of other amino acids. Very carefully crafted regulatory mechanisms have evolved in order to achieve that result. We do not make our own tryptophan, we get it from green plants; they have to adjust the catabolism of these nutrients accordingly. So this chart is only the beginning of the complexity of metabolism. It only shows the principal nodes; the edges are the catalytic factors which are responsible for the interconversion of one substance into another. Each edge may be one enzyme or a whole chain of enzymes, which catalyze these inter-

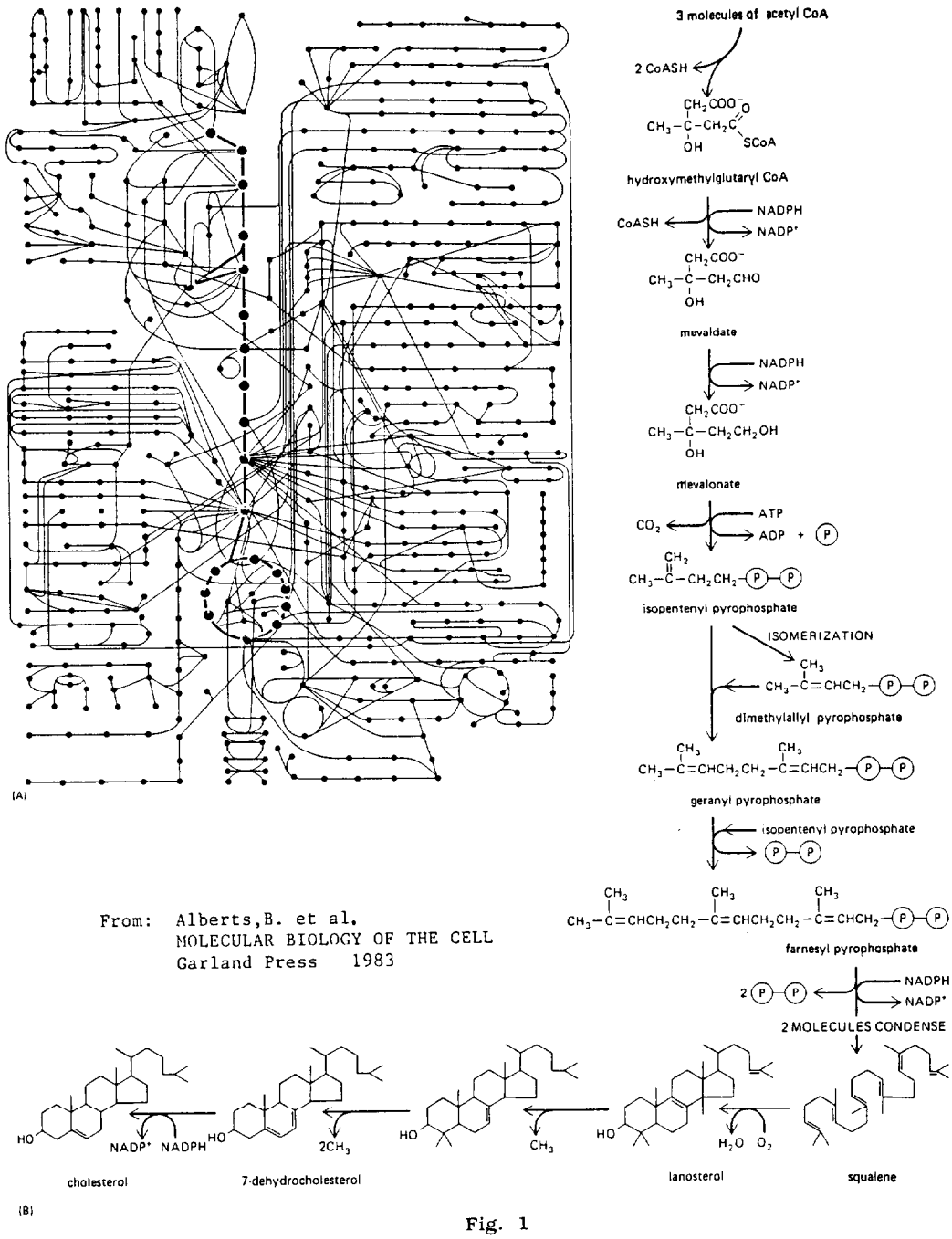

Fig. 1

conversions. Of these we have a few hundred whose actions we can designate. In a limited number of cases we have actually isolated and extracted these substances so that we can demonstrate the catalytic activity of these edges in the test tube. In a still more limited number of cases we have enough detailed information about the structure of these protein enzymes that we can begin to rationalize how they behave, although we are far from a complete theory of the action of any enzyme.

A group of people like you is the very best gathering before whom to exercise a few of the cardinal numbers of biological systems (Fig. 2). These deal very closely with the question Dr. Townes asked as to whether

A Primer on Human DNA

- 3,000,000,000 units in a human cell (uncoiled = 2 meters)
- 10,000,000 genes possible
- Information content comparable to a full set of *Encyclopedia Britannica*
- Only about 1% active (rest 'selfish'?)
- 100,000 proteins probably make up the constituents of the human body
- About 1000 proteins have names AND can be guessed to be present in the body
- About 100 proteins have been isolated and definitely characterized in humans
- About 10 human proteins have *medical uses* today
- If DNA were scaled to width of magnetic tape, it would stretch round the world
- Until recently, DNA was the most asymmetric physical object in the universe. (Now there are commensurate optical fibers 10^7 meters long)

Fig. 2

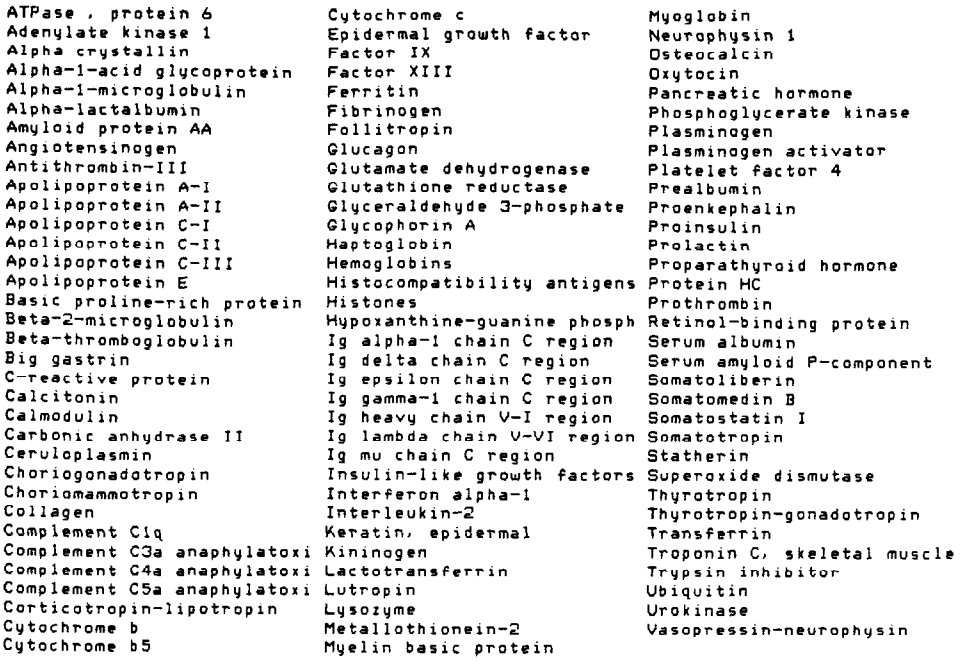

Fig. 3

there is a practical finitude to these expansions of knowledge. If you run out of particles and physics, I suggest you start looking within the cell: there will be some more to do for some time to come. One of the marvels of contemporary biological science is that we have a metric of complexity of the human organism at the level of DNA. Each of us carries in every nucleus of every cell of our body approximately three billion nucleotide units. These are the base pairs of the Watson-Crick double helix. The three billion units, when extended into that double helix form, would range 2 meters in length, tightly coiled into a little sphere approximately 5 micrometers in diameter. This would be enough to encode for ten million gene products if each of them were informationally active, an information content approximately that contained in a few sets of the Encyclopaedia Britannica. This is the genetic code that is inscribed in the zygote and in every cell of our body produced by it.

Happily, for investigative purposes, only about 1 percent of that DNA is believed to be informationally active, so what we have to look forward to is a roster of 100,000 proteins, give or take a factor of 2, which make up the human body. Of those 100,000, where there is informational coding, we can guess at the names of 1000; about 100 have actually been isolated and definitely characterized in the human organism. I actually compiled a list. (All of this has to be done on the computer, which makes it very convenient to bring this information to you; see Fig. 3.) So, at the protein level, we can inventory 1/1000 of the constituents of which our bodies are formed.

We have a glimmer of the mode of action of a few dozen of these. There is a good story about how hemoglobin works, as well as a few others. Others have regulatory functions in controlling the rates at which certain edges will be functional in the graphs that I just indicated. They may have many, many other interactions, one with another, of which we only have a glimmer. Just to discover these one at a time is an enormous side of the enterprise. To comprehend the total is one of the major challenges of all of the electricity that we are going to be able to muster for the next 100 years.

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