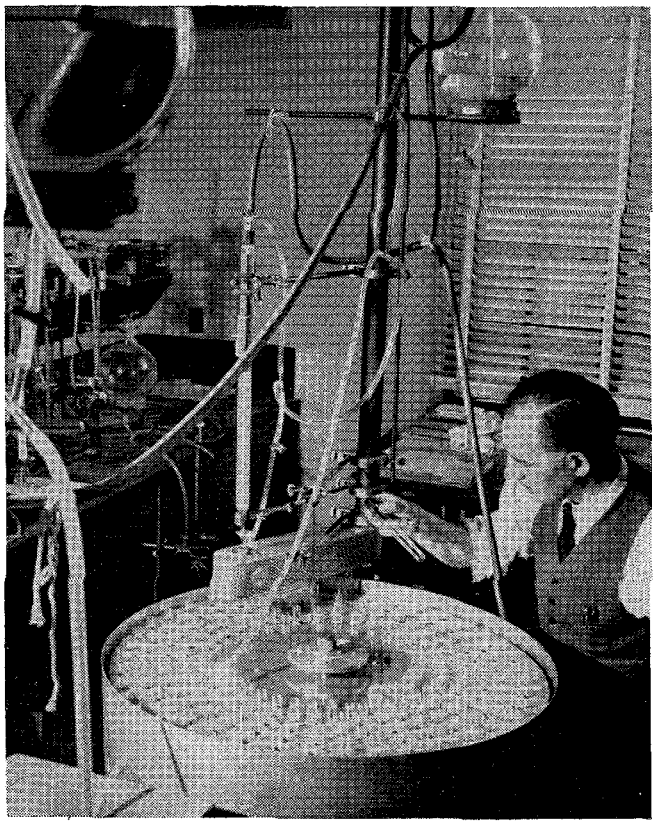
Dr. Henry Borsook,
Caltech Professor
of Biochemistry



BIOCHEMISTRY

A Report on Research in Progress

THE FOLLOWING ARTICLE *is a transcript of a radio interview with Dr. Henry Borsook, Caltech Professor of Biochemistry. Dr. Borsook, an M.D. who chose biochemistry as a career, is doing research on the biological synthesis of protein. His research is supported in part by a grant from the American Cancer Society.*

This interview was conducted on the program, "Report to the People," a monthly report from the American Cancer Society, and was broadcast over KABC, Los Angeles, and the ABC Coast and Mountain Network.

That your work is supported by the American Cancer Society, Dr. Borsook, means, I take it, that it has a bearing on the problem of cancer.

Yes. To explain how, I think I had better say a word or two about my subject in general. The aim of biochemistry is to know what all the substances in a cell are, what happens to them, and how, in their combined action, they make a cell or an organism do what it does. Of all the substances in animals and plants, proteins and nucleic acids are most characteristic of living things. *From the time I began to study biochemistry I have* been mainly interested in proteins.

What is so special about proteins?

Of all the solid matter in our bodies there is more of protein than of any other class of substance. The bulk of muscle, liver and all other organs is protein. We think of protein as meat and eggs. But hair, finger nails and toenails, horn are proteins. Skin is mostly protein. That is not all. The machinery of all cells, substances we call enzymes—without which little, if anything, would go on—all enzymes are proteins. Some hormones, like insulin and ACTH, belong to the class of proteins.

And you are studying the biological synthesis of protein?

Yes.

By that you mean how cells build proteins up?

"Build up" is the exact phrase. Proteins are very large molecules built up from 20 different kinds of bricks called amino acids. Hundreds, even thousands, of these 20 different kinds of bricks go to make one protein molecule. Given 20 different kinds of bricks, using a hundred or more of any one kind, you can make structures of many different shapes and sizes. Most animal proteins have pretty much the same average composition. Yet they carry out quite different operations. The differences between them reside in that their constituent amino acids are arranged in different patterns and in structures of different sizes. There is something in cells which guides them to making these complicated patterns always the same. Not only that, but they make pretty much the same number of each kind of pattern.

Does each cell do all its own construction of protein?

We think so; but really we don't know whether each cell does the whole job itself, or only finishes the job.

Do you mean that it may be that when we eat foods, such as meat, milk and eggs, the cells in our bodies take the proteins in these foods and just change them around a little bit?

No. When we eat these foods the whole, fine, complicated structure of their proteins is wrecked in our stomach and intestines. They are broken down to their constituent bricks, the amino acids. Digestion is, chemically speaking, a wrecking operation. For example, a baby: At first it gets only milk; the milk proteins are broken down in its stomach and intestines to amino acids; these now pass into the blood; each tissue takes from the blood amino acids to build itself. That is how, from milk, a baby makes muscle, skin, all its organs, blood, everything. That is how milk is transformed into a growing baby. It is the same with us.

How do you mean "it is the same with us"? We aren't babies; we aren't growing.

Although we aren't babies, we are continually renewing ourselves. You know that hair grows all our lives. But what I mean is more deep-rooted than that. For example, every seven days about half the liver has broken down and rebuilt itself. It rebuilds itself as fast as it breaks down. In some tissues this process is faster than in the liver, in others slower. Take again the picture of a protein molecule as a large brick structure. What goes on in the body is as if bricks were flying out all the time, and immediately being replaced by the same kind of bricks in exactly the same places. The result is that on ordinary analysis the body appears not to change. And yet it is always changing and it always remains the same.

How, then, can you tell, if it always appears to remain the same?

By the use of what we call labeled molecules. The molecules are literally tagged. The amino acids are synthesized with one or more of their carbon atoms radioactive. The radiation we use is too weak to have any significant effect in the cell; but we can measure the radioactivity after isolating the substance in which it is. The amount of radioactivity is a measure of the number of molecules so tagged.

When we want to measure the changing process of protein synthesis we begin with a tissue in which none of the molecules are tagged. We then introduce the tagged molecules, which otherwise are exactly the same as the ordinary kind. After a short time, the protein is isolated and the amount of radioactivity as measured in a Geiger Counter gives the number of tagged molecules in the tissue protein; and this tells how many of the fresh tagged molecules have gone in to take the place of an equal number that have gone out. It was by this method that we learned that the liver, for example, is breaking down and rebuilding itself all the time.

How does the body know how to balance breakdown and rebuilding so nicely?

That we don't know and are trying to find out. In normal growth, building up in all tissues is a little faster than breakdown. In wasting diseases there is more breakdown than building up. In recovery from these diseases, in the repair of wounds, only in tissues that were damaged is the building up faster than breakdown. A growing tumor or cancer takes amino acids that come from food protein and the breakdown products from other, normal cells, and uses them for its own growth, at such a rate that the body as a whole slowly loses. A small fraction of the loss in the body as a whole is represented by gain in tumor mass. Just how a tumor or cancer drains material away from other, normal tissues we don't know yet. It isn't the size of the tumor, because this often happens when the tumor is quite small, relative to the whole body mass. Something has happened to the regulation.

In your studies of protein snythesis how do you go about it? What tissues do you use?

We use immature red cells. This enables us to study protein synthesis outside the body under conditions that we can control much better than in the whole animal. In the right salt solution, kept at body temperature, these cells remain as intact and as alive as in the body. Protein synthesis is relatively fast in these cells, two or three times faster than in the liver.

Do you think that what you learn from these immature red cells may apply to tumor growth?

Yes, for two reasons. The first is that biochemistry of the last thirty years has found that all living forms, whether animals, plants, or micro-organisms, carry out even very complicated processes in the same way. In fact, much of the machinery, the enzymes, is identical and the steps in the process are the same. So whatever we learn from one tissue, even a normal tissue, probably holds in a growing tumor. And so all biological studies, in all biological forms, throw some light on the biology of cancer. The second reason is that immature cells and cancer cells, biochemically, resemble each other. The similarity is closer between them than between normal adult cells and cancer cells. The fact that immature cells and cancer cells are growing, that is, increasing in mass, while normal adult cells are not, points up the similarity.

How do you think your findings on protein synthesis in immature red cells may throw light on tumor growth?

A cancerous growth is abnormal. We can't understand how it is abnormal unless we know something about the normal. Most of the growth is of protein. Having learned some of the salient features of protein synthesis

in normal tissues, it will then be possible for us to examine whether cancerous tissues are in any way different, i.e., abnormal. This may seem a slow and roundabout way to attack the problem, but the whole history of science teaches that, in the long run, it is best to get fundamental information. By this I mean first getting information that is generally applicable, and then applying this fundamental knowledge to a specific problem. This is a faster way of getting results than by just trying things.

One of the reasons for choosing immature red cells to work with is that it is not difficult to get a lot of them whenever you want them. Another reason is that we can isolate easily for these cells a single, well-defined protein, in this case hemoglobin. We can learn more about the synthesis of proteins in general by learning how the special pattern of one is put together. Dealing with a mixture of patterns, one can't learn anything special.

This is rather general. Can you tell us anything specific from your own work?

I can tell you about some of our most recent findings. But I want to make clear and emphasize that I have no idea at present what their bearing may be on the cancer problem. We have found that in blood, liver and organs there are small amounts of certain special substances that stimulate protein synthesis in immature red cells. The rate may be increased two to four times. They are a family of chemically related substances that were not known before. We have learned how to isolate them in a relatively pure state, and how to identify and measure them in very small amounts. We can measure a millionth of an ounce. And we think we have a pretty good idea of their chemical structure. Now, turning to cancer, either we or others will investigate how much of these stimulating substances is in tumor tissues, whether these tissues have more or less of these stimulating substances, as compared with normal tissues, and whether they are the same kind.

Would you care to speculate on other possiblities from this finding of yours?

Speculation is a precarious business for a scientist talking to a lay audience. His guesses may be taken for predictions, even promises, when they are only guesses, really. Nevertheless, I think I may, without giving a misleading impression, refer to the work of others to indicate how our findings may lead to a new line of exploration. Most biochemical processes are carried out by a special class of proteins called enzymes.

Enzymes are, as I've said, the machinery of the cell. For a substance to be acted on by an enzyme, the sub-

stance and the enzyme must fit together very closely, like a key in a lock. When a key is not quite the right one, you may get it into the lock but then it jams the lock, and you may have a hard time getting the key out.

One line of investigation begun and carried on extensively by many other workers has been to make substances that are very like the natural substances that enzymes work on, but still just a little different. They attach to the enzyme because they fit nearly perfectly, but because they don't fit exactly the enzyme can't do anything with them, and (like the right key in a jammed lock) the natural substances that do fit perfectly can't get to the enzyme. So, because the enzyme can't operate, the whole process stops, and if it persists for long the cell will die.

The stimulators you have found operate by fitting on to enzymes that build up protein?

In a way we don't yet understand the enzyme needs these stimulators to join the amino acids together to make a whole protein. Knowing the chemical structure of these stimulators, it may be possible for us to make others like them, but just a little different, to see if certain enzymes needed for protein synthesis can be blocked. The difficulty is to find such an unnatural substance that will block the enzymes in cancer cells much more effectively than those in normal cells. If they block the enzymes in normal cells, then they will be poisons and of no therapeutic value.

What are the chances of finding such a substance that will block enzymes synthesizing proteins in cancer cells more than in normal cells?

I don't know. My guess is that the chances are not great. It will take a lot of work, testing a great many such compounds. And the silver bullet may be found in some quite different line of investigation. Penicillin was first found in a study in which the investigator had no thought of an antibiotic in mind. In fact antibiotics were entirely unknown then.

I hope I have made clear the need for investigating the cancer problem on a broad front, and the usefulness to the cancer problem of studies of processes in normal tissues. This is the reason that the American Cancer Society, advised by leading scientists of the country, is supporting investigations along many lines, with normal as well as abnormal cells and tissues, in order to get the necessary fundamental information to attack the cancer problem in an informed, intelligent way.

I will conclude with one prediction. The fundamental information so gained will be found useful not only in the cancer problem but in the understanding, prevention and treatment of other diseases.