

W H A T M A K E S B A S I C
R E S E A R C H B A S I C ?

BY HANS SELYE

WILL TEACH YOU SO MUCH!



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What Makes Basic Research Basic?

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With the discovery--popularly expounded in his book *The Stress of Life*--that the human organism has innate defenses against fatigue, pain, and disease, Dr. Hans Selye influenced the entire course of modern medicine. His findings have been ranked beside those of Pasteur, Koch, and Ehrlich. A Viennese by birth and a naturalized Canadian subject, Dr. Selye now directs the Institute of Experimental Medicine and Surgery at the University of Montreal.

Until recently most of us engaged in basic research saw no reason to explain our work or our motives to the public. We felt there was something vulgar in discussing our peculiar problems with people not fully prepared to appreciate all the fine technical points and that it would be an immodest bid for attention. We felt that the singular world of basic research could be understood only by those who live in it. To attempt to explain it in lay language seemed hopeless and even

childish--as futile and naïve as to expound the current problems of the American automobile industry to an African chieftain who had never seen either America or an automobile. Now, however, as Bertrand Russell puts it, "Not only will men of science have to grapple with the sciences that deal with man but--and this is a far more difficult matter--they will have to persuade the world to listen to what they have discovered. If they cannot succeed in this difficult enterprise, man will destroy himself by his halfway cleverness."

The basic research of today produces both the lifesaving drugs and the destructive weapons of tomorrow. Its outcome will affect everybody, and in a democracy whose people decide how wealth shall be distributed everybody shares the responsibility of developing the nation's scientific potential. But how can anybody vote intelligently without some grasp of the problems bearing upon that development?

Bridging the gap between the scientist and the general public will not be easy. The former will have to learn to translate his problems into a language meaningful to the layman; the latter will have to realize that, however simplified, the essence of basic research cannot be assimilated without mental effort.

What is basic research? Charles E. Wilson, the former Secretary of Defense, defined it as what you do "when you don't know what you're doing," a sarcasm presumably intended to justify the inadequacy of financial support for basic research. More commonly, basic research is thought of as the opposite of "practical" research, the kind that can be immediately applied. This suggests its disassociation from man's everyday problems. The development of weapons, television sets or vaccines is obviously practical. Studies of the inner temperature of distant stars, of the habits of infinitely small living beings, of the laws governing the inheritable coloration of flowers, all seemed eminently impractical--at least when first undertaken. They were viewed as sophisticated pastimes, pursued by intelligent but somewhat eccentric, maladjusted people, whose otherwise excellent minds had been sidetracked by a queer interest in the farfetched and useless.

I remember my own reaction in school when I was taught how to estimate the inner temperature of distant stars. Cunning, I thought, but why should anybody want to know? When Louis Pasteur reported that germs might transmit diseases, he was ridiculed. Fancy a grown man worrying about being attacked by bugs so small no one could see them! When the Austrian monk, Gregor Johann Mendel, amused himself by observing the results of crossbreeding red with white-flowering peas in the monastery garden, even his most farsighted contemporaries failed to imagine the momentous implications.

Yet, without basic knowledge of the behavior of distant stars, we would not be placing satellites in orbits today; without knowledge about bacteria, there would be no vaccines and antibiotics; and without those observations on the inheritance of color in peas, modern genetics--with its importance to agriculture and medicine--could never have developed.

Such considerations must arouse public interest in basic research. They are bound to make people realize that the more manifestly sensible and practical a research project, the closer it is to the commonplace we already know. Thus, paradoxically, knowledge about the seemingly most farfetched, impractical phenomena may prove the likeliest to yield novel basic information, and lead us to new heights of discovery.

Some insist that basic research must proceed in the same spirit as "art for art's sake," and should not be appraised by its practical applicability. Yet, in defending this view they usually argue that even the most abstruse research may eventually yield practical results. It is odd that the study of the impractical should have to be justified by its potential usefulness.

Others maintain that not even potential usefulness should enter into our assessment of important basic research. It was the eminent English chemist and physicist, Michael Faraday, who, more than a century ago, made the remark so often quoted by these ultra-purists--"What is the use of a newborn baby?" But not everything important to us need be useful in the accepted sense of the word. At the same time, utility is inseparable from man's assessment of what is important. Perhaps in this still un-

prejudiced, pliable core of a human being we sense a possible future helpful friend. In any case, a baby is useful because we can lavish our love on it--and without love there can be no happiness. Pure art--a great painting, a piece of music--is useful, since it lifts us beyond the preoccupations of everyday life, bringing us peace and serenity. Bearing these facts in mind, I am inclined to define basic research as the study of natural laws for their own sake, irrespective of immediate practical applicability --with emphasis on the qualification "immediate."

But, to me, the need is not so much to define basic research as to distinguish between greater and lesser basic-research projects. This distinction is of immense importance, both to the investigator who requires a standard by which to choose his subject and to the public who pays for his work in the hope of profiting by it. The future welfare of humanity depends largely upon the recognition of first-rate basic research in its earliest stages, when it lacks practical applicability. No nation can afford to subsidize every kind of research, and many a fertile, creative thought has had to be buried stillborn because no one wanted to risk money on it until its value was proved.

Let me emphasize that only the kind of research usually designated as "basic" is true discovery. What follows is development. The former kind is basic, or fundamental, precisely because every other kind of research develops from it. It strikes us as impractical and the work involved as haphazard, because wholly original observations cannot be planned in advance. To do so the observation would have to be anticipated on the basis of previously known facts, and hence could not be wholly original. That is why most of the completely new leads are accidental discoveries

made by men with the rare talent of noticing the totally unexpected. These form the basis of all premeditated research projects--the kind I call development.

It may be argued that any attempt at early recognition must be foredoomed, since the unexpected cannot be anticipated. To some extent this is true. Of course, there is no reliable yardstick with which to compare the relative importance of basic-research projects, but I believe it possible to formulate certain principles which can serve as general directives. Think of them not as rigid

measurements, but rather as a kind of course in science appreciation, helping us to recognize and enjoy creative scientific thought.

To my mind, it is characteristic of great basic discoveries that they possess, to a high degree and simultaneously, three qualities: they are true not merely as facts but also in the way they are interpreted, they are generalizable and they are surprising in the light of what was known at the time of the discovery.

It may seem redundant to say that the newly discovered facts must be true, but by this I mean they must be both correct and seen in proper perspective. Otherwise the finding may be misleading because of the inferences drawn from it.

Not long ago a chemist tried to make a compound that would diminish appetite and cause loss of weight. After years of study, he succeeded in producing a drug that conformed to his theories concerning the structure this kind of substance should have. He then tested the compound on rats, cats, dogs and monkeys. As he expected, all the animals ate very little and lost weight. In a paper describing his findings, he explained why he thought a drug of such chemical structure would act in this manner. In the conventional sense, his findings were true. In my sense they were false. We know that almost any damaging substance will diminish appetite, and his substance was damaging. The author neither admitted nor denied this. He did not recommend his drug for human use. Still, his paper implied applicability. Hence, his finding was untrue by implication. Had he realized that his compound decreased appetite only because of its damaging effects, he would not have bothered to write a paper about it. Few scientists knowingly publish untruths, but many scientific papers contain such untruths by implication.

Yet, even if a finding is true by all standards, it may not be important. I recently read a paper describing the mean weights of the internal organs of laboratory rats. The author's facts were correct; he had killed hundreds of animals to build up a highly significant series. But the resulting information was of limited importance, being neither generalizable nor surprising. It is not generalizable, because we can deduce no general laws from it; it does not necessarily apply even to rats of a different strain. In-

deed, in the researcher's own stock, the organ weights probably would have varied had he changed the diet or the temperature of the laboratory. Nor is the information surprising, because it was evident at the start that the mean weights could be determined by measurement. This sort of work not only fails to qualify as "basic research" but it has not even been practically applied to anything.

The best you can say for it is that it might be applicable by somebody needing these figures as a standard of comparison for original investigation, but then his would be the basic research. Scientific literature abounds in such reports. The authors customarily protect themselves by stating self-righteously that they draw no conclusions from their observations. But this is not good enough. Facts from which no conclusions can be drawn are hardly worth knowing.

This sort of finding may be made accidentally, but usually it results from what we call "screening," and, hence, falls into the class of development rather than of discovery. Such screening might be used by the clinician testing a num-

ber of cortisone derivatives, more or less at random, on patients with rheumatic diseases. Cortisone itself is a hormone that has been found effective in such cases and the clinician merely wants to screen related compounds to see whether one of them might prove more effective. Again, all this is development of previously known facts, not original, creative research.

We are guided in such work by so-called "deductive reasoning," which helps us foretell certain things about an individual case from a previously established generalization. If most cortisonelike compounds are effective against rheumatism, any newly prepared member of this group looks promising. But the deduction itself cannot be generalized. The work may be of immediate practical importance, leading us perhaps to the ideal antirheumatic compound, but, in the highest sense, it is sterile, because the observation is complete in itself, offering little likelihood of further discoveries.

Unfortunately, this drab kind of research is the easiest to finance, because of its immediate applicability to practical problems which can be precisely described in a routine application for funds.

Other observations lend themselves to "inductive reasoning," the formulation of general laws from individual observations. But this feature does not suffice either. To illustrate, it was shown that the first ten hormones, the products of endocrine glands, that could be prepared in pure form were all white. From this, we could generalize. We could foretell, with a high degree of probability, that the next five hormones to be synthesized would also be white. So they were. But what of it? Who cares what color future hormone preparations will be? The appearance of the substances is irrelevant.

Here, then, was an observation both true and generalizable, but lacking the third essential quality of important basic research, the quality of surprise; that is, the unexpectedness of the discovery at the time of making it. Most body constituents are white when purified; hence, it is not surprising that hormones should be white.

I recall my astonishment on learning in medical school that certain pathological growths in the human ovary, the so-called "dermoids," may contain teeth and hair. A medical curiosity, but not generalizable--at least not at present. All we can say now is that occasionally, even without fertilization, an egg in the human ovary may develop into a monster consisting mainly of hair and teeth. This much has been known ever since the seventeenth-century German physician, Scultetus, gave the first complete description of what he called "morbus pilaris mirabilis," the astonishing hair malady. Martin Luther referred to it as the "Offspring of the Devil."

For centuries, physicians and laymen alike have been fascinated by the anomaly. But it opened up no new vistas of research. The reason is, I think, that the observation was made too early. Even today we are not equipped to evaluate it. It is like a strange island remote from the charted areas of human knowledge. Perhaps, later--when we know more about fertilization, about reproduction without fertilization and about the "organizers" that direct the formation of human structures--the

"Offspring of the Devil" will become an angel guiding us to the solution of Nature's mysteries. But merely being aware of the oddity avails us nothing. Scultetus saw, but he did not discover.

Laymen rarely appreciate the fundamental difference between seeing and discovering. America was not discovered for mankind by the Indians, nor by the Vikings who came in the tenth century, but by Christopher Columbus, who established a permanent bridge between the new and the old worlds. It is the process of unifying, the "creative synthesis," be it even of longknown facts, that alone can promote true understanding and progress.

As Hans Zinsser, the great American bacteriologist, put it: "So often, in the history of medicine, scientific discovery has merely served to clarify and subject to purposeful control, facts that had long been empirically observed and practically utilized. The principles of contagion were clearly outlined and invisible microorganisms postulated by Fracastorius about a hundred years before the most primitive microscopes were invented; and the prePasteurian century is rich with clinical observations that now seem a sort of gestation period leading to the birth of a new science."

This essential distinction between seeing and discovering is illustrated by the development of insulin, the pancreatic hormone with which we treat diabetes. In 1889, the German physiologist, Minkowski, and his associate, Von Mering, surgically removed the pancreas in dogs and thereby produced diabetes. They did not, however, realize that the disease resulted from a lack of pancreatic insulin, and their finding did not stimulate much progress until 1922, when the Canadian, Frederick Banting, and his co-workers extracted insulin from the pancreas, and showed that this hormone can actually abolish not only the Minkowski type of experimental diabetes but also spontaneous kinds.

It subsequently turned out that, some seventeen years earlier, the French physiologist, Marcel Eugène Emile Gley, had performed experiments similar to Banting's. He had even described them in a private communication deposited in a sealed envelope

with the Société de Biologie. Only in 1922, after Banting's publication, did Gley permit his letter to be opened. It fully supported his claim to have first found insulin. But he received little credit. As Minkowski remarked during an international symposium on diabetes, after Gley violently protested against the injustice of it all, "I know just how you feel. I could also have kicked myself for not having discovered insulin, when I realize how close I came to it."

Obviously, Gley did not recognize the importance of what he saw. He failed to generalize from it, to tie it in with clinical medicine; otherwise he would not have been satisfied to deposit his findings under seal. In fact, it would have been criminal to do so, had he realized that he thereby signed the death warrant of the thousands who succumbed from diabetes for want of insulin. None of Gley's work was comparable in importance to the discovery of insulin. Why did he put it aside, if not because he failed to understand its significance? It is easy to deposit private communications about things we are not sure of, and unseal them when somebody else proves that we were on the right track. To my mind, Gley not only failed to discover insulin but he also proved that he could not do so. By chance he saw it, but he did not discover it.

The element of chance in basic research is overrated. Chance is a lady who smiles only upon those few who know how to make her smile.

Let us consider a really great achievement of basic research: The observation by Alexander Fleming that penicillin can kill varieties of disease-producing microbes, at dose levels tolerated by man. This is true both in the fact itself and in the obvious inference that penicillin can protect against infections. It is also a generalizable observation. It has enabled other investigators to discover many useful drugs derived, like penicillin, from molds. And, finally, it was surprising to find that molds, which we regarded as contaminants, can have a curative value. Only a highly creative, original mind, one that can completely free itself from established ways of observation, can make such a discovery. Many bacteriologists had seen that cultures of microbes are

spoiled when exposed to molds, but all they concluded was that molds must be kept out of such cultures. It took a stroke of genius to see the medicinal promise of the basic observation.

Basic research must, of course, penetrate deep into the unknown without losing contact with known realities. To accomplish this, the scientist must have a peculiar kind of intuition. Perhaps his most important characteristic is a nega-

tive one. He must lack prejudice to a degree where he can look at the most "self-evident" facts or concepts without necessarily accepting them, and, conversely, allow his imagination to play with the most unlikely possibilities. In the process he requires serendipity, the gift of finding unsought treasures. (The word was coined by Horace Walpole, in allusion to the fairy tale of The Three Princes of Serendip, who were always discovering, by chance or by sagacity, things they were not seeking.) He must have the power of abstract thinking. Planned steps into the unknown must first be made in the mind, without the concrete support of experience.

The basic researcher must also be able to dream and have faith in his dreams. To make a great dream come true, the first requirement is a great capacity to dream; the second is persistence--a faith in the dream. As for intellect, I repeat what I said in *The Stress of Life*, "Pure intellect is largely a quality of the middle-class mind. The lowliest hooligan and the greatest creator in the field of human endeavor are motivated mainly by imponderable instincts and emotions, especially faith. Curiously, even scientific research--the most intellectual creative effort of which man is capable--represents no exception in this respect. That is why the objective, detached form of an original scientific publication or of a textbook falls so ludicrously short of really conveying the spirit of an investigation."

Finally, the basic scientist must have all these qualities in the proper proportion. Too great a propensity for abstract thinking may turn him into a bookworm addicted to sterile ratiocination. Too much faith in his dreams can hinder the verification of concepts by experiment. That is why the line of demarcation between the rare genius and the eccentric inventor is often seemingly so indistinct. To the uninitiated, there is much in common between crack brains and cracked brains. Yet it is important to recognize the promising basic scientist early, when he needs support for the development of his singular gifts. The nation's culture, health and strength depend primarily upon its creative basic scientists--the "eggheads."

What is really meant by this now-so-popular term? To my mind, an egghead's main endeavor is to search for the kind of truth that can be verified by experience. The researcher employed by industry may be excellent at his particular job, but usually he does it for a living; rarely is it his main purpose in life. (Of course, if it is, he qualifies as an egghead.) An intellectual may accept a fact unquestioningly on the authority of books or scholars, without feeling the urge to verify it by experience. The theologians who must accept dogma on faith, the teachers who try to disseminate knowledge, the lawyers, engineers or physicians, who apply truths, are all intellectuals and may be very valuable people. But they are not eggheads.

We can no longer afford to allow scientific genius to remain idle for want of money. Nor can we afford to concentrate all our attention upon the physical sciences because of Sputnik. Nuclear war may or may not come, but the war against disease and death from "natural causes" is on now.

The problem, however, goes beyond the mere provision of financial aid to our scientific elite. To adapt ourselves to the spirit of this century we must reassess our whole philosophy and our sense of values. Just as the Stone Age, the Bronze Age and the Iron Age were characterized by the use of stone, bronze and iron, so our era will undoubtedly go down in history as the Age of Basic Research. Man has gained unprecedented power through investigation of natural laws. This power can lead us to the brightest chapter in human history--or the final chapter.

We must ask ourselves one supreme question, and act according to our answer. Shall we fight each other or shall we fight Nature? Men attack men in bitter competition for profit. Nations attempt to exterminate other nations in the struggle for dominance. The real enemy is Nature. Yet we can make Nature our servant. Let man measure his strength against an adversary worthy of the strongest contender, an adversary at once power-

ful enough to challenge us all and rich enough to provide us all with priceless treasure as long as the universe endures.

There are those who create wealth and those who fight over it. The former are undoubtedly the happier. Wealth is the byproduct of their passion. The scientist loves research. The great industrialist does not create jobs for his workers and products for his customers merely to enrich himself, nor does the artist paint chiefly for fame. To these creators the pursuit is not tedious toil, nor are the rewards the ultimate aim of existence. To them wealth and recognition are largely the unexpected, though gratifying, secondary result of what they do for its own sake.

Nature seems to have so arranged matters that her essential objectives are camouflaged, as it were, so that they impress us as the unplanned consequences of something we enjoy doing. (Few people enter the nuptial chamber with the production of a child as their main preoccupation.) That is why the public at large, and often the scientists themselves, do not feel that honors or material rewards are called for. Yet, the man of creative mind must be accorded a privileged position, not as payment, nor because he needs encouragement, nor even to help him in his work, but as the most effective means we have to demonstrate our appreciation of human values to the next generation.

We must educate our children to understand that from now on man's great wars will not be fought with muscle. His battles will not be won by the glorious, intoxicating, momentary courage to face danger and die for a cause. Our children must learn that the great victories in peace and war will be won by warriors of a different stamp, men of intellectual vigor, and by the sober, persistent dedication of their entire lives. They will have to learn that it is far more difficult to live than to die for a cause.

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