IF I WERE YOUR AGE

Hans Selye

University of Montreal

I was greatly honored when I received the invitation of the *Dalhousie Medical Journal* to write a Graduation Note. I must confess, however, that I became somewhat worried when I arrived at the lines instructing me to write "around 2000-2500 words and deal with what you would do if you were, this spring, graduating in Medicine or, what is much the same thing, what advice you would give a young medical graduate."

My trouble is that, if I were given this second chance, I would do exactly what I have done the first time some 40 years ago. This would land me (in the year 2007) just about where I am now. I could hardly write 2000-2500 words just to say that I failed to profit by experience and it would be a tragedy for Canada's health if I could convince this year's graduates of Dalhousie to abandon the practice of medicine and spend their lives doing basic research, as I did. Still, research is the fountainhead from which medical practice derives strength - its progress will undoubtedly affect you all, whatever you chose to do - hence, I can perhaps best acquit myself of the task assigned to me if I outline some of its most pressing problems.

THE CROSSROADS

Today, basic research is at the crossroads. Should we study molecular biology or broad-scale correlations on a supramolecular level? Of course I am deeply impressed with the intricacies of molecular biology. Who could fail to stand in awe before such outstanding achievements of the mind as the elucidation of RNA, DNA, ATP, ADP and all the other complex biochemical entities of life that have now become so commonplace as to require acronyms to save time in daily conversation? This line of research needs no protagonist and if I remain one of the few defenders of old-fashioned supramolecular biology, it is only because nowadays, almost no one else is willing to do it any more and I would hate to see the art become obsolete.

As I look around me, I see virtually no more simple, general practictioners of medical research. Even the few who have managed to survive tend to camouflage their true colors by adopting a "pseudomolecular" lingo. Instead of heredity, they will speak of genes, instead of calcification, of calcium-hydroxylapatite nucleation, lest they should appear to be woefully behind the times.

Yet, it seems to me that no matter how much we shall learn about the most intimate mechanisms of biologic phenomena, we shall always need the old-fashioned holistic approach. For the all-embracing view, we shall continue to depend upon the broad scale correlation of simple observations in which the chips are handled as units, although we know that in fact, they are intricately structured complexes. Indeed, the closer we come to breaking down the chips into subunits of subunits, the more the bruised bits become artefacts - mere ashes of life.

WHO SHOULD BECOME SCIENTISTS

One of the questions I am most frequently asked by prospective scientists is: "What are the qualifications needed for a career in basic medical research?" I am not competent to discuss the talents needed for other types of research, and, of course, even in my field opinions differ enormously. Intelligence, imagination, curiosity, perserverance, the powers of observation and of abstract thinking, initiative, technical skill and many other gifts are singled out as being especially important. Can one generalize? The morphologist will need the power of visual observation much more than the biostatistician; the experimental surgeon or the developer of new instruments will depend more on technical skill than will the medical historian.

However, the cardinal qualification required by all scientists is creativity. In the context of his environment and special subject, his success may be more or less dependent upon technical skill, the gift of observation, or the ability to get along with associates; but there is no doubt that the rarest and most precious gift is the power of original creative thought. It characterizes only the elite among scientists and it is astonishing to what extent this one great gift can compensate for a host of deficiencies in other respects.

The power of original creative thought reflects an independent freshness of aspect, initiative, and resourcefulness in approaching a subject. This in turn depends upon imagination, the power to form a conscious idea of something not previously perceived in reality. It requires vision, discernment and foresight, a hunch of what is important at a time when its importance is not yet obvious.

It is odd that in science, the most intellectual activity of man, the first and most decisive step should depend upon vague hunches. Yet that is how it is, we might as well admit it. Man is so proud of being bright that he named himself *homo sapiens;* and yet a dog's nose can often find a murderer where all the intellect of the best criminologists fails. Some of the most impressive original creations of mankind have been in the arts. Yet, few artists would feel ashamed for having to rely more on feeling than on intellect. Why should the scientist be so reluctant to admit that the same is true of scientific creativity?

Having said this, let us be sure not to put any mistaken value judgements on the relative importance of intuitive discovery and intellectual development in our sense of these words, that is of problem finding and problem solving. What good would it be to know that the adrenals exist if this discovery had not been followed by carefully planned investigations on the structure and function of these glands or the isolation and synthesis of the useful hormones that can be obtained from them? This second stage of research has required much more intellect and a much more complicated methodology than was needed by Bartolomeo Eustachio to find the glands in the first place.

Far be it from me to overrate discovery in comparison with development as regards either the intellectual satisfaction or the practical advantages that can be expected from them. Besides, they are wholly interdependent, but the qualifications needed for discovery and development are not the same. Therefore, the modern fashion at our Universities of directing all the most gifted students in the life sciences towards molecular biology is not justified.

Now that we have fairly well defined what we mean by discovery and development. let us agree on some terms to designate the scientists who practice these arts.

"PROBLEM FINDERS" AND "PROBLEM SOLVERS"

Certain scientists depend mostly on instinctive feeling for the ways of Nature, a keen sense for importance behind observations and for correlations on a broad scale; let us call them the *problem finders.* They are interested essentially in new configurational wholes, rather than in structural detail. The second are the *problem solvers.* They start with something already known and try to take it apart to understand its composition and mechanism. Hence, they must lean heavily upon the use of logical analysis and the methodology of chemistry and physics; these are really exact scientists because, in essence, they merely apply the results of the exact sciences to biology. I was tempted to call them the "exact biologists" but, of course, this would be wrong because biology is not an exact science. It is very instructive to apply chemistry, physics, and sometimes perhaps even mathematics to biology, but the more you dissect living matter into its basic constituents, the further away you get from life. The chemist who synthesizes a hormone, the physicist who elucidates the crystal structure of bone minerals, supply data important to biology. Yet they are not biologists, no more than the gunsmith is a soldier, or the telescope designer an astronomer.

You will say there is no reason why the analyst, the problem-solving kind of exact scientist, could not also make a discovery just because he is looking at one particular aspect of life, a minute structural detail or a single biologic process. Of course he could; but the more sharply we focus on detail the more we reduce the likelihood of unexpected discoveries by the "peripheral vision" of things that turn up accidentally where we are not looking for them. It would hardly have been possible to discover anaphylaxis, yellow fever or the phenomenon of homograft rejection, by the use of the electron microscope or of cell chemistry.

THE BIRTH OF PROBLEMS

Let us now see whether careful planning and sophisticated technology have played an important part in the most decisive first stage, the birth of great biologic discoveries.

One of the most important milestones in the history of medical research, an observation which probably saved more lives than any other, was the discovery of antibiotics. It has been described as a "triumph of accident and shrewd observation". Among these compounds, penicillin was the first which could be put to practical use. Here is the history of its birth:

While the English bacteriologist, Sir Alexander Fleming, was engaged in research on influenza, a mould had accidently developed on a staphylococcus culture plate and created a bacteria-free circle around itself. Fleming immediately concluded that some principle (he called it penicillin) produced by the mould kills bacteria; this substance, he thought, might be used to combat infections.

You may say that anyone faced with the same fact would have come to the same conclusion, but history shows that this is just not so. Actually, the same observation had been made with different moulds and bacteria many times before, yet no one thought of making any use of it. At first sight, a mould appears to be such a dirty thing that it would seem unbelievable that anyone would want to put it on a wound or inject it into a sick person. Moulds usually grow on spoiled food, and we have become so accustomed to consider them as damaging that only a highly creative, original mind, one that can completely free itself from established patterns of thought, could make such a discovery. All the earlier bacteriologists who had noted that cultures of microbes are spoiled when exposed to moulds, merely concluded that moulds must be kept out of such cultures. It took a stroke of creative genius to see the promise of this basic observation.

I could cite many additional great landmarks in the history of the life sciences, but instead, let me tell you a little about my own work. For this choice, I have several excuses: first, I can discuss my findings from firsthand observation; second, to make my account instructive, I can be harshly critical of some flaws in the problem finder's approach; third, it permits me to contradict the current feeling that most biologic phenomena that can be discovered unaided by our sense organs, without planning, have been described long ago.

I am often asked just what made me think of the Adaptation Syndrome, or Stress concept, as it is frequently called. In retrospect, after so many years, it is rather difficult to single out precisely the beginning of a long trend of thoughts. As far as I can recall, nonspecific reactions always held a singular fascination for me, because they were generally neglected and rejected from the focus of attention. I clearly remember one of the first lectures in internal medicine which I attended in 1925 as a medical student. We were shown several patients in the earliest stages of various infectious diseases. As each case was brought into the amphitheatre, the professor carefully pointed out that the patient felt and looked ill, had a coated tongue, complained of more or less diffuse pains and aches in his joints, gastrointestinal disturbances with loss of appetite and weight. Less constantly there was fever, an enlarged spleen or liver, proteinuria, an inflamed tonsil, a skin rash, etc.

Then he enumerated a few "characteristic" signs which, should they subsequently appear, would help the diagnosis of a specific disease. These, we were told, are the important changes to which we must give all our attention. Until they develop, not much can be done for the patient, since without them it is impossible to formulate a definite diagnosis or recommend efficient therapy.

I could understand that our professor had to find specific disease-manifestations in order to identify the particular pathogens from which these patients suffered. This, I realized, is necessary so that suitable drugs might be prescribed, medicines having the specific effect of killing the germs or neutralizing the poisons that made these people sick. But, novice that I was, it impressed me much more that so few signs are actually characteristic of any one disease, while most of them are common to many, wholly unrelated maladies - or even to all diseases.

Why is it, I asked myself, that such widely different pathogens as those of measles, scarlet fever or influenza, share with a number of drugs, allergens, etc., the properties of producing the above mentioned "nonspecific syndrome"?

I could not understand why, since time immemorial, physicians should have attempted to concentrate all their efforts on the recognition of individual maladies and the discovery of specific drugs suitable only for the treatment of individual diseases, without giving any attention to the "mechanism of just being sick". Surely, if it was important to find remedies against one disease or another, it would be ever so much more necessary to learn something about the mechanism of being sick, and the means of treating that "general syndrome of sickness", which is apparently superimposed upon all specific diseases! This, in essence, is what the Adaptation Syndrome is all about. All I did before was a prelude, and all I did later, a postscript of this central topic of my scientific life.

INSTINCT vs. INTELLECT

Today, the use of the word "instinct" in connection with research is taboo; it smacks of sheer guesswork which, by definition, is not research. Let me admit that it is precisely this supercilious attitude towards instinctive research that I deplore. Even in medicine the simple approach of the general biologist, the naturalist, or clinician, is not yet and never will become obsolete. His exploration of life is aided much more by keen observation and an instinctive feeling for Nature than by complex instruments and elaborate planning. Forty years in the laboratory, and a critical analysis of research psychology, have unskakably convinced me of this.

It may be objected that there is no point in encouraging neophytes to become problem finders instead of following formal courses and learning sophisticated techniques useful for problem solving, because intuitiveness cannot be taught. This is true, but only to a point. The blind cannot be taught to paint, nor the deaf to play music; but in science, as in the arts, innate talent can be suppressed by excessive obligatory course work and routine technologic training - just as much as it can be developed by personal apprenticeship under experts in action whose style is worth emulating. Besides, the problem finder's career is not for the masses in any case, since the gift for it is rare and moreover, each new discovery occupies countless problem solvers for many years. I do feel, however, that we should make every effort to maintain the tradition of the naturalist by raising a few of them, say one percent among all those who plan to specialize in biologic research. These few will do much for their colleagues by opening up new fields, by finding new problems that can be solved through the application of the exact sciences. These are the few for whom the inscription above the entrance to our Laboratories at the *Université de Montréal* will be a constant reminder. It says:

"*Ni la puissance de tes instruments*
Ni l'étendue de tes connaissances
Ni la précision de tes plans
Ne pourront jamais remplacer
L'originalité de ta pensée
Et l'acuité de ton observation."
(*Neither the Power of your instruments*
Nor the extent of your learnedness and the
Precision of your planning
Can substitute for
The originality of your approach and
The keenness of your observation.)

with the Compliments

of

The P.E.I. Medical Society