Markle Lecture

The Business of Discovery in the Medical Sciences

Charles B. Huggins, MD

This essay is shoptalk concerned with the craft of medical research; it is a credo of creativeness. A century ago Claude Bernard described his approach to science wherein experimental medicine was conceived to be a specific discipline defined as the application of physiology to pathology: "Physiology must be constantly applied to medicine."[1] Claude Bernard's classic work has had a continuing and profound influence on successive generations of investigators, but Emerson said, "Each age, it is found, must write its own books; or rather, each generation for the next succeeding."[2]

It is a pleasant vocation to do experiments while teaching young people how to find out new and beautiful and helpful things—how to do elegant Science. It becomes a philosophy because excellence in work engenders excellence in life. These remarks can be reminiscent of the traditional professor of economics who, it is alleged, knows everything about money but doesn't have any.

The leitmotiv in our work has been an attempt to learn how to experiment in the most fruitful manner. It is a progressive and unending evolutionary process. One constantly improves experimentation with thoughtful experience just as a virtuoso betters himself and increasingly gains deeper knowledge of music from a lifetime of ceaseless practice. As a beginner I profited from the common wisdom and mutual support of a classical university department. Later membership in a department seemed restrictive and a small autonomous research institute for advanced study in the medical sciences in the university was found to be more fulfilling since it permitted greater freedom for my activities. An institute is desirable when protracted activity is required of specialists in many disciplines. A department trains students and confers the doctorate; an institute trains professors and grants no degrees. Teaching is heavily involved in both department and institute; always the young apprentices are present but only a few at any one time in our lab because, like Ehrlich, I believe that great events do not occur when many pigeons are flying about the room.

From the Ben May Laboratory for Cancer Research, University of Chicago.

Read before the 13th annual Markle Scholar meeting, Mont Tremblant, Quebec, Sept 21, 1965.

Reprint requests to 950 E 59th St, Chicago 60637 (Dr. Huggins).

Doing Science in the universities is one of the most pleasant of the vocations of man. It is consuming and a delight. One must give everything but receives much in return. One pits his wits against apparently inscrutable Nature, wooing her with ardor. Nature is Blind Justice who cannot recognize personal identity. She can refuse to speak but she cannot give a wrong answer. She is an unsophisticated buxom lass who can be cajoled but not forced; Her vocabulary consists of only three words—yes, no, and perhaps. It is the genius of research to frame a question so simply that a conditional answer is prohibited.

And there are the young people who give far more than they receive. Youth is the tractable age; in the young it is easy to kindle enthusiasm, *le Dieu intérieur*, which is essential to discovery. From age 18 to 32 the imagination is a dry forest and a small flame can set the whole thing on fire; usually after age 35 it is too late to begin creativity because the woods of the imagination are soaked. There is plenty of emotion in our business. Inevitably one develops affection for all of the co-workers united for the purpose of common study, both the men and the women. And coffee in gallons is drunk; instant coffee seems to be the lifeblood of the investigator in the medical sciences.

Early in the game it seemed that an economic description of what we were trying to do might be helpful to all of the group. A motto was coined: "Discovery is Our Business." We yearn for discovery of effects and also of talent. Our shibboleth has utilitarian purpose—it is a notice for the young men to use golden years of privilege without responsibility to grow tall in Science by finding out. Emerson said, "It came to him business; it went from him poetry."[2]

Eventually the young people leave the lab to assume responsibilities of university professors with their own units in some discipline or other—which area is of no importance because with classical training in methods of enquiry one can learn the technical jargon and tricks of any given specialty in a few weeks. Parting is sorrow, but it is not a total departure—it is metastasis. The young professor-elect takes part of the laboratory with him, its spirit, and also he knows some pitfalls to avoid in the new climate.

There is a strong Baconian influence in experimental medicine. In *Novum Organum* old Bacon formulated the doctrine "Truth and utility are the very same things."[3] But some truths are more useful than are others; it is not often helpful to remember a telephone number, since changed, of 20 years ago.

A component of research, crucial in importance, is recognition of a noble problem; only this will yield the highest gratification in its solution. A talented investigator has a nose for a good problem. This instinct is inborn; also it can be acquired at an early age. A problem assumes nobility in Science when it yields a paradigm, a conceptual scheme which influences the age by provoking activity.

The needs of the people are not of cardinal significance in determining what problem we shall select for investment of our effort. But urgency of a medical problem should be kept in mind. The research workers must be cognizant that they are beneficiaries of the hopes and prayers of mankind for solution of heavy problems of disease. Medicine can profit from work done in many fields. Take cancer research: doubtless the Curies did not dream that successive refinement of purified fractions of pitchblende vis-à-vis increased concentration of radioactivity to yield radium eventually would lead to practical treatments of cancer in man.

It is of paramount importance that a project should be both interesting and manageable. Either the investigator's equipment, mental and technical, must be adequate for his task or he must be able to grow into the necessary techniques and processes. It is perpetually rejuvenating each year to learn a new and tough technique, some rigorous method.

To reiterate, a problem in Science can be solved in only one way; a question is proposed in so simple a manner that Nature must provide a categorical answer. Solution of big problems demands patience in long efforts. For difficult problems a series of connected interrogations (rungs of the ladder) is necessary; as a result of the answers (its uprights) the most difficult problems become simpler as solutions emerge.

New areas of investigation can be introduced only through a conceptual scheme, but the investigator discovers truth by activity alone. Science is ruled by the duumvirate of idea and technique. Claude Bernard[1] said, "The head is powerless without its executive hand." In Medicine the idea frequently comes from observation of the vivid but essentially simple displays of Nature at the bedside and in the laboratory; both theaters are of high importance for understanding and for developing treatments of human disease.

An old saying holds: "Science and art are twins and both are the children of fantasy."

> Tell me where is fancy bred
> Or in the heart or in the head
> How begot, how nourished?
>
> —Shakespeare, *The Merchant of Venice*

Science is not cold and unfeeling—it is highly personal. In discovering, one becomes emotionally bound up in his problem. Head, hand, and heart are all involved in creativity in the medical sciences and the combination enables us to recognize a good problem; its scent elicits a characteristic physiological reaction which gives one confidence in his ability to solve the research.

When Newton was asked how he made his discoveries, he said: "By always thinking unto them."[4]

There is a time to start a research and a time to let go. A problem must be abandoned when the law of diminishing returns becomes restrictive. In the Uncertainty Principle, Heisenberg proved that it is impossible to know the position of an elementary particle *and* its velocity. This means that the nearer one gets to a final answer the more evasive the solution becomes. We develop our physiological responses which tell us when to let our problem go and then to start something new.

How To Start a New Medical School

In 1927, clinical medicine at the University of Chicago was aged and ailing. It was designated Rush Medical College and was located seven miles from the university campus. There were two incurable defects in this arrangement. If you must walk a block outside to consult a colleague you resist the temptation; miles through traffic become a safari. To quote a remark of H. G. Weiskotten: "Nothing cements like brick and mortar." Second, medicine was taught by amateurs and semiprofessionals, by very distinguished clinicians who were busy and immensely successful in their service functions. With a part-time medical faculty, private clinical practice was first in interest whereas productive scholarship trailed.

With these considerations, the University of Chicago decided something had to be done, either to abandon instruction in medicine or start afresh. It built a hospital de novo on its campus. The Billings Hospital opened on Oct 1, 1927, with about 175 beds, a green staff of 30 young doctors, and four students. Clinical material consisted of one patient who had been hoarded carefully through the summer. This was the first full-time salaried staff of any university clinic. In the surgical faculty there was one senior surgeon, no more. There was plenty of time for leisure. What was to be done? The first task was to give momentum to the young faculty.

The single mature surgeon on the faculty and its leader was Dallas Burton Phemister. Essentially his philosophy was Confucian—the aim of life is continuous self-improvement; also, one's group is more important than one's self. On the opening day, the young surgeons appeared at the decent hour of 9 AM, but never again—the Chief had been working since before 8 AM. Phemister taught us by example with his door open at all times. And he would come around at 8:15 to ask, "What have you discovered today?"

Each week the surgeons had three departmental conferences on (1) clinical cases if any was available; (2) research that we had done or knew about; and (3) surgical pathology.

My doom was sealed in the unlikely locale of conferences on surgical pathology. These were usually dullness unmitigated. We sat on stools packed in a small room with a projector of microscopic slides showing static things on a poorly illuminated screen. One day Phemister briefly described the Neuhof effect[5] which was news to all of us. Harold Neuhof, surgeon at Columbia University in 1917 (it was wartime), did research on dogs with an immensely practical aim. Neuhof was concerned with extensive defects in hollow viscera, similar to war wounds of trachea, stomach, bladder, and others; can these be repaired by autografts of fascia lata? Nature answered Neuhof in the affirmative; epithelium grew over the graft forming a beautiful new lining in the patched organ. But bladder responded in a way different from all others. Invariably bone formed in the patch of fascia used to repair the hole in the bladder. The formation of bone was attributed to a combination of (1) necrotizing effect of urine (urea; pH; tonicity); (2) deposit of calcium phosphate in the dead tissue by the well-known effect of incrustation of salts of urine on a foreign surface; (3) transformation (*Umwandlung*) of calcification into bone. The explanation was logical, ingenious, and wrong.

A first experiment was to repair with fascia a defect in dog's bladder which contained no urine, the ureters having been permanently transplanted to the skin. To our intense delight, a large piece of bone formed in the patch in the ever-empty bladder[6] the influence of urine in this effect had been excluded categorically. Next, we found that epithelial lining of the urinary tract of dogs induced bone whenever it was transplanted to fascia. Contact for the first time of two soft tissues which never calcified separately, uroepithelium and fibroblasts to which they are unaccustomed, inevitably transforms the latter into osteoblasts in dog. The change of fibroblasts into osteoblasts is invariable; it is permanent and accordingly it is a somatic mutation. It was the first discovery of induced change of one cell into another kind of cell. The experiment is big—bone the size of a large coin is formed invariably and within 21 days. The phenomenon was not called transformation and it did not have much impact; now the effect is remembered by fully five people and likely no more. But some of the learned and faithful quintet study the phenomenon each year; the transforming principle has not been discovered.

The chief value of this spectacular experiment was its introduction of a young worker to the delight of discovery and the tingling thrill of research. The inoculum was contagious; it persisted and reproduced itself as a habitual craving to find out.

Out of gratitude and to demonstrate control of Nature, I transplanted vesical mucosa in such a way that the induced bone formed the rather crude letter **P** which, after harvesting, was presented to Phemister in a velvet-lined box. Experimental medicine can be employed to make one's Christmas remembrances. This business of evoking the formation of bone in an initial of the name of his Chief was not disadvantageous to a young man attempting to make a favorable impression.

Phemister was strongly opposed to parochialism in his faculty and he had a pleasing way of intimating permanent tenure of one's university appointment. "How would you like to spend a year in European clinic or laboratory—we will supplement your salary with $3,000 for travel." Soon I found that occupying the stands of famous clinics was very dull indeed, so that was abandoned. In Europe one learned to be fluent in foreign languages, gazed on distinguished people, saw the famous sights drenched in history—all worthwhile, but one yearned for the lab.

A Travel Year

A high spot in the *Wanderjahr* was a pilgrimage to Warburg in Berlin-Dahlem. Warburg in 1930 was isolating nucleotides from yeast cultures with the aid of the critically important 340-$m\mu$ wavelength, whose significance in reduced pyridine nucleotides he had discovered. It is an understatement to say that I was profoundly impressed by the great happenings in the Warburg lab.

Wandering through the campus of the Kaiser Wilhelm Institute, I chanced into Harnack Haus for lunch with a clever and good young biochemist, Frank Dickens, who was working with Warburg on the rather mysterious enzyme glyoxalase. Dickens discerned immediately that the question that was burning the brain of his table companion was; "Why is blood made mostly within our bones; why the predilection of hemopoietic tissue for the intraosseous cavities?" Dickens immediately had a suggestion which was genial in felicity. "Why not try Robison at the Lister Institute and he has just been elected to Royal Society." Within two hours an airmail letter was on its way to Robert Robison, FRS, with appropriate congratulatory remarks on this greatly deserved honor; two days later I had notice of my acceptance in the Robison lab, and the stay turned out to be a wonderful experience.

Robison was a talented organic chemist who knew how to do experiments and he adored making discoveries. In 1930, he had just isolated glucose-

6-phosphate from yeast and had oxidized it with bromine to 6-phosphogluconic acid. These esters of Robison's were of key importance in the isolation of nicotinamide-adenine dinucleotide phosphate by Warburg. Coincidentally they led to discovery of the pentose shunt of glucose metabolism in which Dickens was involved importantly. Quite remarkably, Robison had predicted the presence in rich concentration of alkaline phosphatase in growing bone and in hypertrophic cartilage and the prediction was verified by experiments. Quickly I realized that I was amidst genius in the presence of these remarkable investigators.

In the Robison lab, I was immersed in the delights of organic chemistry. In experimental medicine the value of a research is determined by its content of exact sciences, chemistry or physics; without such aids little of value can be accomplished.

Robison had a very small school and he had never had a pupil with the training of a physician. And he was lonesome for a listening ear and for responding comments. One clarifies his thoughts by explaining them aloud to others. Strengths and weaknesses of ideas in science are amplified by returning again one's thought to his brain through his own ear as well as by the comments of the listeners.

In the Robison lab we came at 10 AM and worked at the bench without lunch until 4 PM. Then came a meal called afternoon tea, unnecessary for calories but indispensable in the lab for spiritual and educational uplift. After our discussion often we went to some lecture, always selected for importance by Robison; following that there was much talk of the lecture and the speaker while returning to Chelsea on the upper deck of a bus.

Conversation with Robison was exclusively shop-talk. Questions were asked turn and turn about. There was one dialogue, perhaps it was the most important one, and this sticks in mind:

H: "What would you do if you found on your lab table (Robison disdained an office) an envelope left by an angel labeled 'Cure of cancer is stated within'?"

R: "I'd tear it up without opening. I'm interested only in my own thoughts."

Nature of Science

The reply of Robison illustrates the egotistical component of Science. One can read for an hour in his library and learn many facts which he did not know, but these are facts discovered by others. It is not learning as such that gives the highest intellectual satisfaction. The egotistical component is to see vistas that no man has perceived hitherto. And this has pragmatic value because it brings out the best in man. When one discovers a fact he regards it as his own—man assumes a proprietary interest in a natural phenomenon.

What is applied and what is basic research? A common and facetious reply has been: "That which you do is applied; my own work is basic." The question is posed badly—frame it as enquiry. All search for new knowledge is basic, all application of knowledge is technology. Much basic research can be done on medical wards.

Medical research is unusually demanding insofar as an elegant solution of a difficult puzzle is not an end sufficient unto itself. Medical research is not complete until the solution which has been achieved impinges on the lives of the people. In the final analysis the measure of a physician is his therapy. When one discovers something which prolongs life and relieves suffering, it remains a meaningful legacy to the race which will persist forever.

What is the optimal number for a research unit? It is alleged by Paul Weiss that a huge governmental agency looked into this in trying to determine whether it was 10 or 1,000 scientists or what number. An arbitrary quotient was devised in which numerator was utility of a project and denominator the number of persons employed. The optimal number turned out to be 0.76, in round numbers, 1 person. I think that this number is off by a small factor, say 2 or 3; science thrives with a team of a few talented and young scientists aided by clouds of technicians. With technical assistants instructed by the scientist and, accordingly, trained to meet his standards it is hard to get a wrong answer. Technician does not know what result to expect; young doctor is tempted to engage in unconscious fiddle-faddle to please his chief. The snowstorm of technicians are paid exorbitant wages; all members of the team are given extravagant praise for honest work done well. They go through the wringer of work with permanent tenure of position implied. I cannot divorce them and they do not leave me.

Self-Pilferage of One's Time

The pendulum oscillates inexorably, but how little does man value his most precious commodity, his time. Steal his car, man screams with outrage. But one abets self-pilfering of his priceless hours. Gladly and unwittingly we steal our own time with trivialities. Scientists welcome being kidnapped from their only important source of discovery, the lab table.

Office Desk.—Foreign visitors repeatedly inquire: "When we call on an American professor why do we always find him seated at his desk?" The correct answer is that office is cozy and it takes one away from the rigors of the lab table. Chair-bound, one steals his own time.

Administration.—Frequently one hears the wistful complaint, "I cannot do lab work because I am running a large department." This is conscious or unwitting escapism from the reality of science.

The administrative head of a university department has only three proper functions. (1) He can teach by setting standards for his juniors. (2) He can be a good listener and encourage. (3) He can select the personnel, which, incidentally, is one of the most subtle of the arts. But there are rules for selection of faculty; the most important is to hire only those who are capable of excitement over discovery of elegant effects. One selects only those smarter than one's self; let the head of a research unit select its faculty and turn over all other administrative functions to two competent girls. The administrative assistants handle the resource of the lab and supervise its expenditure. No instrument is considered to be expensive if it is used; apparatus costing a few cents is prohibitively expensive if it is unused. The young ladies write the annual reports since no one reads them, but to ensure this the documents are made very long and highly technical and they are prepared with the aid of scissors and glue.

Scientist-in-Flight.—At the airports and pleasant holiday resorts of the world one finds many scientists relaxing from the rigors of flying through the air on public affairs, scientists-in-flight. So many hours are wasted wrangling or drowsing in committee when something true and beautiful and useful could be found out in the lab—one is stealing from himself.

Sir Arthur William Currie, a famous Canadian soldier, was elected principal of McGill University in 1920. Soon thereafter he said, "I know what to do with a hen that won't lay, but what's to be done with sterile academics?" It might be well to give our unproductive ones resounding titles and let them take over the offices and the desks, administration, committees, and the airplane and let them write our essays.

Thermometer of Progress in Inquiry

When things go well, one hastens to the lab early to spend long and happy hours at the bench. With great expectations, the worker anticipates wonderful things which Nature will disclose to him today. And every day he does something in the lab; no matter how fatigued or how heavily laden with triviality, the worker spends at least a few minutes at the bench.

Discovery evokes a syndrome of symptoms which has not been described earlier. These are long-continuing and include (1) rapid pulse, (2) dry mouth, (3) "butterflies in the stomach", (4) persistent euphoria which causes one to greet friend and unfriend with equal and exuberant good nature and enthusiasm. His companions surmise that the discoverer is thrilled to the very marrow.

Can Creativeness Be Taught?

The answer is no. But the techniques of discovery are contagious to the young before the cerebral arteries become a trifle narrowed. A genius knows intuitively how to discover, and he cannot be held back; it is inborn. With the less gifted but still talented postulants, the high morale of a discovering lab spreads from one to another. Once kindled, the need to discover persists life-long, lifting man far above himself causing him to neglect all other worldly things, so great is its delight—Science has become an addiction.

This study was aided by grants from the Jane Coffin Childs Memorial Fund for Medical Research and the American Cancer Society.

References

1. Bernard, C.: *An Introduction to the Study of Experimental Medicine,* New York: Crowell-Collier Publishing Co., 1961.

2. Emerson, R.W.: "The American Scholar" in *Selected Writings of Ralph Waldo Emerson,* New York: Modern Library, 1940, p 45.

3. Bacon, F.: "Novum Organum," CXXIV, in *The Works of Francis Bacon (Popular Edition) Based Upon the Complete Edition of Spedding, Ellis and Heath: I. Philosophical Writings,* Cambridge, Mass: Riverside Press, 1878, p 156.

4. Andrade, E.N. da C.: *Sir Isaac Newton, His Life and Work,* Garden City, NY: Doubleday & Co., 1954, p 35.

5. Neuhof, H.: Fascia Transplantation into Visceral Defects: An Experimental and Clinical Study, *Surg Gynec Obst* **24**:383-427 (April) 1917.

6. Huggins, C.: The Formation of Bone Under the Influence of Epithelium of the Urinary Tract, *Arch Surg* **22**:377-408 (March) 1931.

HASTE MAKES WORK FOR OPODELDOC.—On the morning of the 17th, Mrs. Brooks's Irish girl Joan fell down the cellar stairs, and was found by her mistress lying at the bottom, apparently lifeless. Mrs. Brooks ran to the street-door for aid to get her up, and asked a Miss Farmer, who was passing, to call the blacksmith near by. The latter lady turned instantly, and, making haste across the road on this errand, fell flat in a puddle of melted snow, and came back to Mrs. Brooks's, bruised and dripping and asking for opodeldoc. Mrs. Brooks again ran to the door and called to George Bigelow to complete the unfinished errand. He ran nimbly about it and fell flat in another puddle near the former, but, his joints being limber, got along without opodeldoc and raised the blacksmith. He also notified James Burke, who was passing, and he, rushing in to render aid, fell off one side of the cellar stairs in the dark. They no sooner got the girl upstairs than she came to and went raving, then had a fit.

Haste makes waste. It never rains but it pours. I have this from those who have heard Mrs. Brooks's story, seen the girl, the stairs, and the puddles.—*Heart of Thoreau's Journals,* O. Shepard, ed., New York: Dover Publications, Inc., 1961.