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Is It Possible to Teach Scientific Creativity in the Pharmaceutical Sciences?

ANECDOTES AND MEMORABILIA

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The Dictionary defines creation as the "act of causing to exist," specifically the act of bringing the world into existence, or some original work of art or of the imagination.[1] Although we attest to the fact that pharmacy students and pharmacists are extraordinary, we cannot claim that they, unlike pharmacy professors, have the god-like qualities necessary to bring the world into existence. We will arbitrarily exclude from our definition the ability to produce romantic novels or works of art. These abilities demand peculiar talents. We limit creativity to the producing of an original work of the imagination an innovation, a previously unthought of solution to a problem, an original thought, discovery, idea, or paradigm.

In the practice of community pharmacy, the opportunity to be creative may be limited to the use of business and organizational talents in optimizing the efficiency, cost, and monitoring of the delivery of the appropriate dosage form to the patient, and devising methods of recording patient histories and monitoring adverse reactions. In the modern era, formulation or compounding is no longer an accepted function of the practicing pharmacist, who is the waiter taking the order in the well-stocked pharmacy, rather than the cook. Only accepted information on dosage, adverse effects, etc., can be divulged to patients or be advised to physicians. Although under Florida law the pharmacist has the option of substituting a generically equivalent product under certain restriction, he cannot diagnose or prescribe. He does not have the legal authority to adjust dosage regimens or tamper with the relations between the physician and his patient.

Hanford has emphasized the synthetic thought processes in creativity. He stressed that apparently unconnected, dissimilar facts are brought into a unified picture; known elements are combined in a new way to give a novel result.[2] Saunders insisted that analytical thought processes are also highly important. A problem should be defined by separation into the component parts that are to be examined for their "interrelationships before the domination of the synthetic processes."[3]

Examples of Creativity

Creative thinking does solve practical problems. Tolls were collected at the bridges and tunnels both on entering and exiting the city of New York. To save the city money in operating expenses and yet reap the same profits, an imaginative individual suggested doubling the fee but only collecting on entering the city, thus halving the collection expenses. It worked, without diminishing the returns at all.

The obese Queen of Serendip promised to give half her kingdom to the subject who devised a comfortable way for losing weight. She rejected gastric resection and intestinal bypassing, compulsory dieting, and sututed jaws, but limited herself to eating gargantuan meals at scheduled times. The one who won the prize fed her unlimited, sickeningly sweet candies before every meal. It worked, but then she had a lot to lose.

Perhaps insight into what constitutes creativity and the creative process can be gained by reviewing the recent "discoveries in science, technology and medicine that . . . rank among this century's most significant historical developments in any field" and that changed our lives . . . fundamentally transforming the way we perceive the world, the nature of the questions we ask and the expectations we hold."[4]

A paradigm is an "example, pattern or model especially outstandingly clear or typical . . ., an archetype . . ."[1] Examples of paradigms are models of the cosmos. Copernicus emphasized the deflating news that the world was not the center of the solar or Ptolemaic system and that the earth was not very special at all.[5] The fixed world of Newtonian physics with a laboratory or observatory on earth being "at rest" was transformed by Einstein to the relativistic world with the laboratory hurtling through space in a universe with light of a finite velocity.[6]

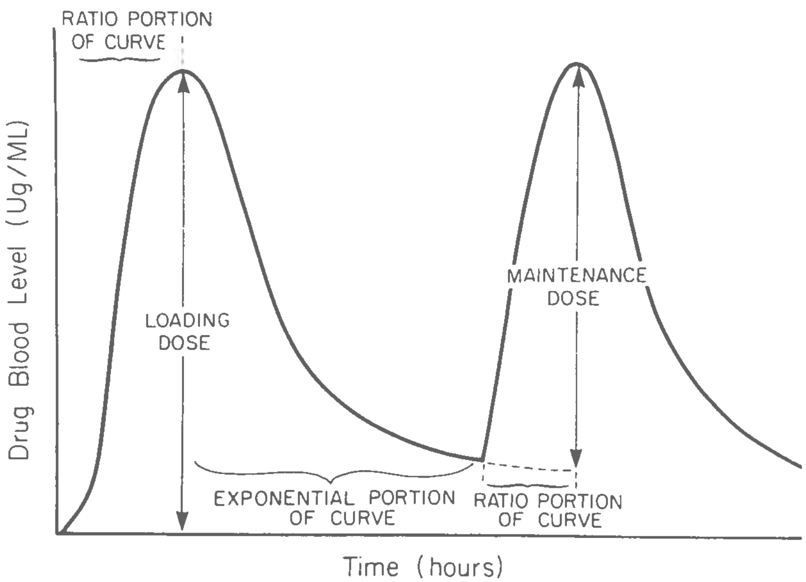

Figure 1. Drug blood concentration time-curve components important for estimating pharmacokinetic dosage adjustments.

You could postulate that God created today's universe only 5000 years ago when, as Bishop Usher, you add up the generations in the Bible. Yet, to explain the observations of an expanding universe, Edwin Hubble deduced the "Big Bang" theory.[7] At the rate of the observed expansion of galaxies, where the velocity of their recession is directly proportional to their distance from us, the time of creation has been estimated as 20 billion years ago plus or minus a few billion. This newer paradigm is consistent with the dating of unstable radioactive elements and the geological evidence that the earth's crust is more than 3 billion years old.[7]

Other bursts of creativity from Max Planck and Albert Einstein gave us the quantum principle of light, that light is composed of discrete quanta, absorbed and emitted only as units. This principle changed the paradigm of light from wave to quantum theory and was the first step to the "unified view of matter and energy emerging in relativity."[6] It led to the E = mc2 equation that gave us the potential evil of thremonuclear bombs and the supreme delight of knowing why the stars shine.[6]

A recent issue of *Science 84* listed those discoveries that changed our lives and transformed the way we perceive the world.[4] Leo Baekeland's "creative chemistry" led to the innovative linking together of small organic molecules to form the large molecules, the synthetic polymers that became our bakelites, nylons, plastic sacks, and wrappings.[8]

Alfred Benet conceived of a mental age, a method to determine it, and provided a quantitative measure of the intelligence quotient, 100 times mental age divided by chronological age. The resulting intelligence tests help to make decisions on military and educational advancement, vocational aptitude, employee selection, clinical diagnosis, and social and personal adjustment.[9] It has been used to argue for genetic determination of intelligence to promote the idea of inferiority for certain minorities. Contrarily, it has been used to demonstrate that these minorities have been socially deprived of the opportunities to demonstrate their inherent intellectual equality. As with all products of our intellectual creativity, the discovery is neither evil nor good in itself, but reflects the use to which it is put. It has been stated that to blame a discovery (whether it be E = mc2 or the Stanford-Binet test) for the nuclear arms race or racial prejudice is "like blaming shipwrecks on the sea."[6]

The vacuum tube, statistical tests, computer, hybird corn, telephone, television, insecticide, automobile, oral contraceptive, laser, electric grid, transistor, blood typing, endorphins—all were innovations that transformed the world.[4]

Many discoveries were negative in the sense that they opposed accepted practice. The old shibboleths and dogmas of medicine had to be *denied* before innovations could be introduced.

Only around 1825 was the question asked as to what would happen to patients with typhoid fever and delirium tremens if *no* treatment were given.[10] Such a study was unpopular, denied the authority of the establishment, and took a century for the answer to be accepted, "untreated patients survived their illnesses at a significantly higher rate than those that were bled, purged and blistered."[10] The backlash to treatment did lead to the "therapeutic nihilism" of the early 1900s, which in its turn was negated by the discovery of the powers of sulfonamides, penicillin, streptomycin, other antibiotics, anticancer drugs, artificial organs, etc. It took new concepts to lead us into these therapeutic revolutions. The realization that the vital processes of bacteria and cancerous tissues could be interfered with and/or terminated without permanent debilitating effects on the host or diseased patient served as the rationale for antibiotic and anticancer therapies. It provided a reason for the development of logical screens to search for such compounds. It provided a reason to synthesize abnormal cousins to normal metabolites and substrates to interfere with such processes.

James D. Watson and Francis Crick "combined insight, hunch, and analysis to build a model of DNA's structure consistent with X-ray images,"[11] a double helix of two intertwined complementary strands, constructed of four nuceloside units that formed a code necessary for an organism's growth and reproduction.[12] This concept introduced the age of molecular biology, genetic engineering, biogenetics that permitted genetic manipulation, duplication, and cut and patching DNA. Thus, insertion of human genes into bacteria, yeast, and viruses could synthesize the products encoded into the genes. Cancer genes were identified and immune systems discovered.[12] Here, again, we could do evil or good. There are possibilities to produce Frankensteinian monsters as well as to cure inherited diseases.

I have not conjured up the "Big Bang" theory, nor discovered E = mc2, nor synthesized a new antibiotic, but even in a less eventful scientific career in the pharmaceutical sciences some degree of creativity has been demonstrated. Some examples from my experiences may be relevant to those trained in the pharmaceutical sciences.

One represents the synthesis of different disciplines of statistics, physical chemistry, and pharmaceutical formulation to solve a problem. To state the problem: product stability in the days before 1950 was determined by monitoring the formulation at room temperature with time. Rule-of-thumb methods to predict shelf-life from accelerated procedures had no theoretical basis. To determine if a product had a shelf-life of three years, it had to be studied for three years, delaying marketing, profits and availability to consumers. There was a need to predict the shelf stability quickly for a dye in a multi-sulfa preparation. Although the sulfonamides did not deteriorate, the color did, and consumers thought the product had degraded. The principles used, by today's perspectives, were simple ones.[13] Rate constants, derived from kinetic plots, were determined at several elevated temperatures (Figure 1). The rate constants at marketing temperatures were predicted by extrapolations based on the Arrhenius' equation (Figure 2). One month of these accelerated studies predicted several years of duration of adequate color to maintain acceptable pharmaceutical elegance. This success led to the prediction of stabilities in multivitamin preparations,[14,15] so that proper overages could be formulated and refrigeration labels omitted (Figure 3). Fancy statistics were incorporated to give confidence limits to stability prediction. These procedures permitted early marketing of products even though new laws demanded labeling with expiration dates.

Characteristics of a Potentially Creative Individual

A survey of creative personages does give us clues as to the characteristics and personality traits necessary in creative individuals. It is generally agreed that the potential to be creative resides within the individual. All individuals possess it, but in varying degrees: the wife who prepares the attractive souffle, the weekend gardener who landscapes his yard, the do-it-yourself carpenter who designs a bench from scratch.

A small child can demonstrate creative mental processes using his available wordly facts. One of my sons, at 3½ years of age, was fascinatedly observing the breast feeding of his recently born brother. He asked, "What's that?" and was informed that his baby brother was getting his milk. He wrinkled up a brow, paused, thought, and after a delay, queried, "What's the other one for? water?" An excellent example, within his limitations, of creative thinking.

Intelligence and intellectual curiosity appear to be significant characteristics of creative people. They cannot accept statements without adequate proof and without almost complete understanding. They have almost a categorical imperative to ask, to know why, to fit details as well as broad concepts into one rationale, one paradigm, one unified theory. In that sense they are mini-Einsteins. Thus, they may resent tight administrative control and may defend their ideas with a persistence that may even tend towards recalcitrance if they deem arguments produced contrarily as not being valid. When all others in an audience fear that to ask a question displays ignorance and inadequacy, these are the ones who ask the definitive questions, inquire for the supportive proofs, or query for explicit meaning. These are the whistle-blowers, the announcers of the emperor's nudity. They do not conform for the sake of conformity.

Motivation for the Creative Process

The creative process demands motivation, an urge to perform, devise, conceive, or to solve a problem. If one does not possess this motivation, one tends to "work to live" rather than "live to work." Without this drive, individuals can be satisfied

with their routine performances and chores. They will conform to existing paradigms and avoid the disagreement with the establishment, authorities, and bosses that may frequently result from proposing revolutionary ideas. These technicians with doctoral degrees follow the research plan programmed by superiors and merely substitute into equations derived by others. They stay forever on the problem given to them by their major professor in their graduate study. They may change the compound but never the study, measurement, calculation, or goal.

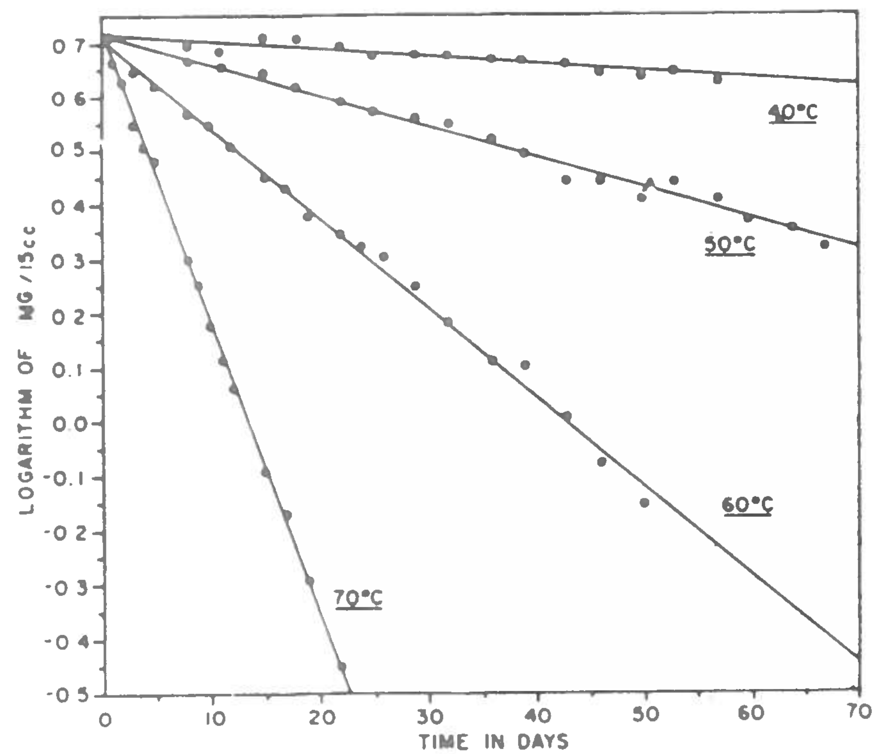

Figure 1. First-order plots of the thermal degradation of thiamine hydrochloride in a liquid multivitamin preparation (A); logarithms of concentration (mg/15 ml) against time in days. Slopes estimate rate constants. Reproduced from Figure 1, Garrett ER, *J Pharm Sci* 1956;*45*:470-3, reproduced with permission of the copyright owner, the American Pharmaceutical Association.

The creative person is less likely to indulge in corridor talk, take the long or even short coffee breaks. He is capable of sustained attention and dedication to his self-directed tasks. He can ignore the noisy environment and his talkative colleagues.

The scientifically creative may tend to possess the varying degrees of arrogance needed to reject, negate, or attack existing paradigms. These can range from achieved self-confidence with courageous perserverance, through irritable persistence to obnoxious obsession with the achievement of their goal whether it be an explanation of a phenomenon, the formulation of a useful product, or the useful application of a principle or machine. They "rock the boat."

Nils Bohr conjured up the orbital picture of the atom as a mini-solar system well before World War I, a system where electrons can jump discontinuously from one

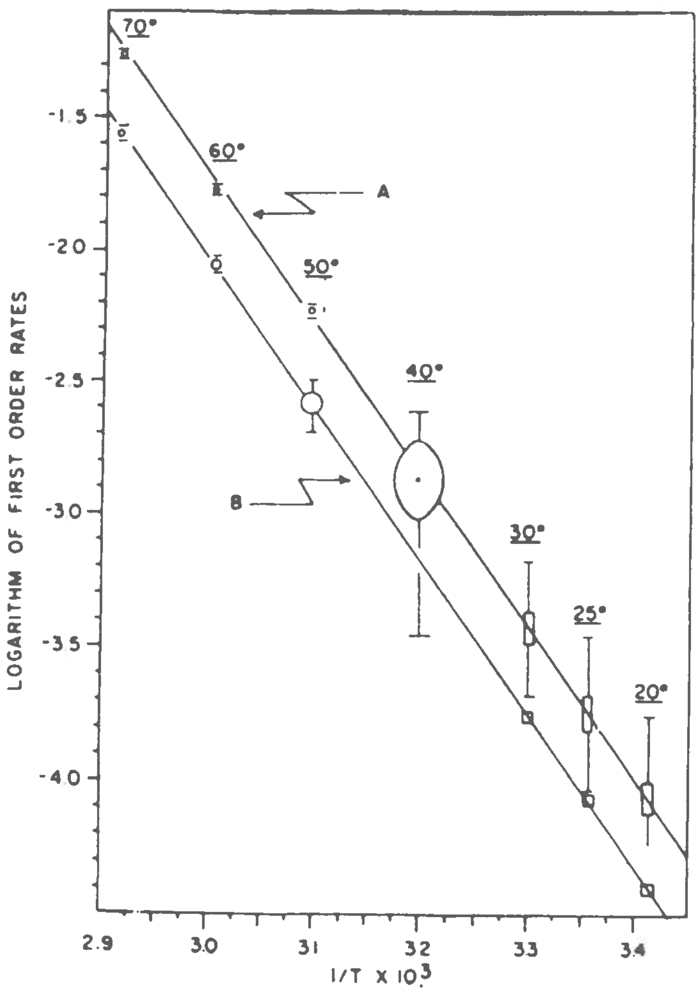

Figure 2. Arrhenius' plots for thiamine hydrochloride. Plot of the logarithm of the slopes of first-order plots (in days) against the reciprocal of the absolute temperature (T) for the thermal degradation of thiamine hydrochloride in liquid multivitamin preparations A and B. The circles represent the standard deviation of an experimental log rate and the rectangles the standard deviation of a predicted log rate. The horizontal lines represent the 95% confidence limits of experimental and predicted log rates. Reproduced from Figure 3, Garrett ER, *J Pharm Sci* 1956; *45*:470-3, reproduced with permission of the copyright owner, the American Pharmaceutical Association.

orbit to another when they absorb or emit a quantum of energy. He thought it was so outlandish that none of his colleagues would accept such an arbitrary explanation even if it did explain atomic and spectral properties and the periodic table. Therefore, he literally tucked the concept into his desk drawer for several years until 1916 when he felt he had achieved sufficient prestige to challenge and replace the existing paradigms and buck the establishment.

Intertwined with this compulsive need to perform, rationalize ideas, or be productive are the normal psychological needs or drives for recognition, worldly rewards, or, in many cases, merely the self-approval that has supplanted the need for social approval, the feeling that the discomfort of not-knowing has been assuaged by solution, that unbearable curiosity has been satiated, that all aspects of the world have been properly cataloged and rationalized.

Initiation of the Creative Process

I do not believe that the creative process is generated spontaneously. There are no sparks or flashes of inspiration without proper choice of and positioning of electrodes in an appropriate atmosphere. The talents must be honed, the techniques and technologies mastered, and the scientific disciplines incorporated into one's intellectual armamentarium. The pharmaceutical scientist must know his chemistry, physics, pharmacology, mathematics, and statistics before he can be creative in the pharmaceutical sciences. Obviously the creative scientist can't be lazy. If he is lethargic, his need and desire must transcend his inertia; else the seeds of his creativity will never be allowed to generate, even less to flower or come to fruition in a full-fledged paradigm, discovery, or idea. Thus, the creative individual usually is a dedicated, energetic, self-disciplined, workaholic, self-starter who is not a clock-watcher and who can do six things at once. He must be able to communicate, speak, and write, or the world will never be informed of what he has created.

The "sharp" or "creative" individual does not produce a novel idea, concept, or paradigm solely from a startling flash of inspiration or from a miraculous revelation. He has organized his prior thoughts, pigeon-holed his information, assayed the potentially significant relationships among diversed facts and ideas and already cataloged those that are fallacious or have failed to show a consistent pattern. Thus, he has uncluttered his mind of the unuseable as he seeks that sequence of thoughts that leads to creativity. The field is prepared for the sowing of the small seed, the "perhaps or if or maybe" that postulates a relationship that predicts certain consequences that seem to lead to the desired goal or explain almost all. The process may appear to be inspired or revealed but such postulates are not conjured by the unimaginative and orthodox nor can they be rationalized by the unintelligent and uneducated. Even Einstein did not instantaneously grasp the equivalence of matter and energy, E = mc2. "He hit upon it unintentionally, almost reluctantly, in the course of months of juggling with the symbols m for mass, E for energy, c for the velocity of light."[6] He was then able to challenge its reliability by showing it was consistent with known observations. He and others were able to predict phenomena on the basis of this paradigm to confirm its utility and temporary validity.

Promotion of Creativity

A simple game can demonstrate how unorthodoxy can promote creativity. To make the winning easier, a clue is presented herewith: "Too many people are bounded or limited by convention."

Draw four consecutive, sequential, straight lines to connect all nine dots in the configuration (a) given in Figure 4 and considered the clue. Most people confine themselves to straight lines that do not go outside the confines of the box as in (b) or (c), since they are psychologically limited by the apparent perimeter. Only careful

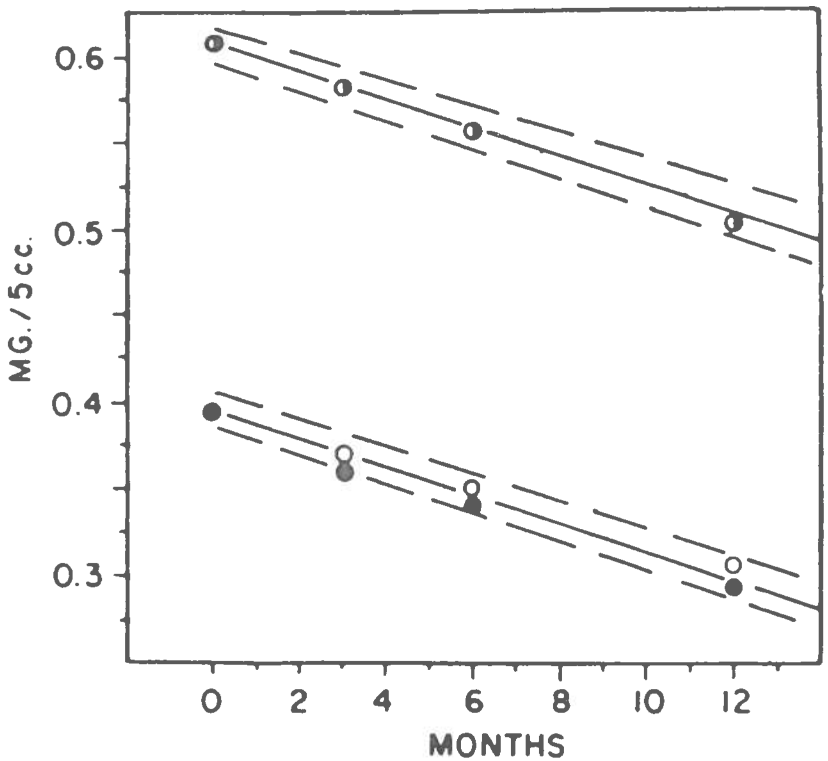

Figure 3. Verification of prediction of folic acid stability at room temperature. The solid lines are predicted thermal degradation rates of folic acid in liquid multivitamin preparation A at 25°. The dashed lines encompass standard error in predicted values and 95% confidence of a single assay. The open circles are data from preparation A, the closed circles are data from a similar preparation B, and the half-closed circles are data from a modified preparation C with increased initial concentration of folic acid and other vitamin components. Reproduced from figure 9, Garrett ER, *J Pharm Sci* 1956;*45*:171-8, reproduced with permission of the copyright owner, the American Pharmaceutical Association.

analysis of the clue and a bit of unorthodoxy permits one to solve the problem by going *outside* the apparent boundaries or limits of the field formed by the outer dots, as in (d).

I do not believe that the educator can instill the personality traits necessary for creativity into students. However, performance capabilities and creative potentials can be fostered, trained, challenged, and given the opportunities to be exercised to their limits.

Social approval can promote creativity. Freewheeling, brain-storming seminars or colloquia should be established where approval is given to the questioner, to the proposer of a new problem, to the reporting of newly published and significant phenomena, to the stating of contrary opinions, and to the presentation of valid criticisms. Too frequently, creativity is stifled by the promoted impression that volunteering and questioning in a lecture or seminar is an indication of the ignorance of the questioner rather than the incompetency of the speaker.

Open-ended seminars should be scheduled so that there is little excuse to rush out of the doors before discussion at the completion of the main talk. I have known Ph.D. graduates, obviously not in our program, who have completed four years of candidacy without asking a single question or making a solitary comment at a seminar. If I am asked to appraise such an individual by prospective employers, I mention it in my references. It is only fair to those who have contributed.

Students should be requested to ask a question of their choice at a given lecture. I have copied a custom of the Canadians and British by informing my graduate and postdoctoral students that one of them will be called on to summarize, well-manneredly, gratefully, and succinctly the gist of what the seminar speaker has presented to present a short critique of its significance, and to present our gratitude for the presentation and stimulation. Since my colleagues are unaware of which one will be chosen, they must listen attentively and analytically, and critically evaluate the message of the speaker as he progresses in the development of his thesis to the presentation of his conclusions. In this manner, they are exposed to the creative processes.

I have forced my graduate students to the limits of their creativity. Obviously, a good major professor would not permit a student to defend his dissertation until he was satisfied that the student were capable of doing so. Thus, I do not attack his present work; that is left to my colleagues on the committee from whom he defends his thesis. The doctoral candidate is forwarned that he must be prepared for my major question. On the assumption that he has a future opportunity to do any scientific endeavor he prefers, he is asked for a research program he intends to follow and its significance, what questions he hopes to pose, and the experimental protocol he plans to use to solve these problems. This theme must not be related to his doctoral dissertation or have been devised or suggested by his present mentors. It should promote and challenge his creativity.

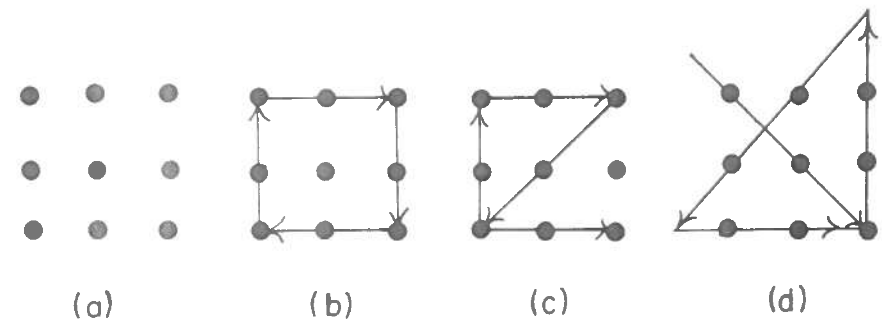

Figure 4. Game of creativity.

Patterns in the Creative Proceese

NEED TO PRODUCE

There are certain patterns to the creative processes. There must be the need or desire to perform or produce, or to solve a problem. It can be self-generated. The curious academician can react to a literature article or a convention talk. It can be imposed by market research's determination of a needed product, as in a pharmaceutical company's research and development, or promoted by a granting agency's statement that money will be provided to satisfy a research need.

ANALYSIS OF THE PROBLEM AND PLANNING THE ATTACK

This need or desire cannot operate in a vacuum. It must be referenced to a particular problem or goal, which must be defined and analyzed as clearly and in as much detail as possible. The answer obtained may well depend on how one poses the questions.

Evaluation of a problem may merely lead to the decision that more data are needed before the appropriate questions can be asked or before the proper experimental procedures can be chosen. This may be feasible only if the time for the accumulation of necessary data or of choosing among alternate routes of solving problems can be shortened. The devising of "quick and dirty," inexpensive, efficient tests to choose the best of alternative pathways with the greatest promise of success to solve a problem is also part of the creative process. These methods should not be so "dirty" or inefficient that they lead to erroneous conclusions.

Although the literature must be searched, summarized, and critically evaluated, it is frequently wise to assess the problem independently prior to this step. Too frequently, creativity may be stifled by full acceptance of what others have done and the way they did it.

I have tried to promote these creative procedures by demanding from research students' descriptions, written and oral, of their proposed problem and the questions to be asked and protocols planned to solve them. They are obligated to give written monthly reports of their progress and plans, to summarize difficulties that they have encountered in their research as well as the reasons for them, and to present new detailed protocols for resolving them in the forthcoming months. At intervals, they will give oral reports to their colleagues at the freewheeling seminars, and, less frequently, elegant presentations before their college peers with semiannual written appraisals of complete results and data. This does not mean that assessments of the problems or the questions to be asked might not change. One of the major stiflers of creativity in the money-grubbing academic grant and contract process is that the prospective grantee writes out his investigative protocol as if he already knew or anticipated the answers, and as if he were irrevocably wed to the experimental procedures he listed.

Contrary to the beliefs of many academic administrators, degree of creativity should not be equated with the magnitude of the grant monies acquired by an individual. As I wrote previously,[16] I do not approve of contact research and do not favor routine control, analyses, or production in academia. They are quid pro quo regimented activities determined by the behest of the contractor. This piece-work stifles innovation, imaginative design, the pursuit of tangents, and the taking advantages of those serendinities that could lead to great discoveries. They frequently encompass activities that are pedestrian and unpublishable in requtable journals. The argument that they bring in funds for other activities is specious. In general, the energies of the contractee are consumed by the supervision of routine technicians doing routine work that brings in funds to hire more technicians to supervise. It is unwarranted competition with the private sector for presumed profit.

This does not mean that funds for pharmaceutical research in academia should not be sought from industry. Drugs that treat disease are to be sold in the market places; there are very few drugs where research activities will not benefit some industrial organization. However, the initiative in the design and control of the study should lie within the professor's bailiwick. There can be no inhibition or restriction

of publishing the truth even if it is financially disavantageous to the source of funds. The independent investigator should submit the protocol and request unrestricted funds to support his research program. Common courtesy would demand that progress reports be given to the private sector, but the right to publish promptly without censorship is a prerogative that must never be abandoned.

A proper analysis of the problem should lead to the devising of several routes to appropriate solutions. It is possible to list branching sequences. If *a* is so, then do *b*; if *a* is not so, then do *c*, unless . . . . Even if the results from the orignial program are ambiguous or lead to inappropriate conclusions, they may suggest a more valid route to determining an answer.

Brainstorming. "Brainstorming," the bouncing of ideas, no matter their wildness or exotic nature, around a circle of innovative and nonridiculing colleagues is an excellent group exercise in creativity. An atmosphere devoid of inhibition, of not knowing what has failed, may allow one person to stimulate the ideas of another, so that ideas are conjured that would not result from one or two persons alone. Thus, a critical mass of research colleagues are needed to promote this chain reaction.

Many of the ideas published from our group have been explored at our open-ended Friday evening seminars, in the seminar room sqecially built in my home, abetted by social libations to release scientific inhibitions and lubricated free-flowing discussions. Thus, in many instances neither the major professor nor the doctoral candidate can take solitary credit for them.

Serendipity. It is even possible that an anomalous phenomenon may be observed that is of greater interest or significance than any possible results from the original problem you hoped to solve. This should not be ignored or forgotten. A scientist is obligated to explain or rationalize unexpected phenomena, not overlook them. This has resulted in many of the quantum leaps to great scientific discoveries.

There once was a Prince of Serendip who left his kingdom to search for something equivalent to a pot of gold at the end of the rainbow. However, his many adventures resulted not in the pot but in the hand of a beautiful maiden that led to a happy married life with an excellent queen, even if she did become obese. This process is therefore termed serendipity. It demands that attention be given to observations as they are forthcoming, that data be plotted, analyzed, and evaluated continuously, that results be rationalized sequentially, to detect the unexpected, the anomalous, the unusual. The investigator that merely collects routine data without careful observation, who automatically disregards the aberrant value as an error without critically evaluating the cause or reason, may never make the great discovery. I have known and disapproved of graduate students who have collected reams of unevaluated data before trying to force them into an ancient paradigm. They would never encounter or recognize the bell-ringing discovery and are wasting their energy tilting at windmills.

The creative person is serendipitous. He may seek one thing and find another, even better. But he has prepared himself with a background of knowledge that permits him to recognize the significance of his anomalous discovery. And he has the personality traits that demand explanation for and rationalization of all his observations. He is the creative individual.

The classic tale of serendipity was the story of Alexander Fleming's discovery of penicillin. There are others. A French pharmaceutical company provided a neurosurgeon with a new anthistamine, which he believed would negate the production of histamine released by streesed, preanesthetically-treated patients. The supposed antihistamines were promethazine and chlorpromazine and Henri Laborit was impressed with the "euphoric quietude" induced by the compounds and recommended them to his colleagues. The drugs' astonishing effects on schizophrenia were observed. Thus modern psychotherapeutic drugs gave genuine relief to the mentally ill and eased symptoms so that hundreds of thousands could be released from mental hospitals.[17]

Oleh Hornykiewicz thought that dopamine might be involved in Parkinsonism. He measured levels in the brains of those that died from the disease and found none of this neurotransmitter! When he gave intravenous injections of L-dopa, the brain transformed it into dopamine and this disease had an effective treatment.[17]

A fascinating exercise in serendipity is the discovery of lithium as efficacious against mania, therapeutic for manic-depression, and prophylactic against recurrent depression. In 1949, a young Australian psychiatrist, who thought that mania was caused by too much uric acid, injected lithium salts of uric acid into guinea pigs and obtained dramatic therapeutic responses. However, it was not the uric acid but the lithium that gave this effect since lithium carbonate gave the same.[17]

Examples of The Creative Process

Analytical thinking defines the problem. Synthetic thinking finds potential solutions. Interdisciplinary blending of the tools and information from various fields, and the drawing together of widely disparate ideas may conjure fresh and unifying concepts. Development of novel paradigms opens new insights and novel approaches to solutions. The literature and consultation with others garner related information that may lead to other potential solutions. The best of these should be chosen and tested for consistency, truth, and attainment of a desired or a recognized goal. If unsuccessful, the new information should be evaluated with respect to the old, and these steps of the creative process should be retread.[3]

This topic has been related primarily to the research-oriented pharmaceutical sciences, but the principles espoused should be generally applicable. During World War II when I was a chemical engineer in Texas, we made synthetic rubber by copolymerizing butadiene and styrene. We were in a hurry to produce and had to do our experimentation with full production. As the new information was obtained, we retread the creative process to obtain the proper product.

The following are examples from our own experiences in the pharmaceutical sciences that may exemplify creative processes. The goal was to determine the plasma protein binding of tetrahydrocannabinol (THC), the active constituent of marijuana. Unfortunately, THC sticks to everything. If one pours an aqueous solution of THC from one glass into another in series, there is no THC in solution after a few pourings. Thus the classic procedures of equilibrium dialysis, ultrafiltration, and ultracentrifugation had the THC stuck to the membranes or cells. Thus, there was no free or unbound drug in solution or permeating the membranes.

Brainstorming devised different procedures. One old-fashioned idea was to distribute THC between plasma and an organic solvent with a known partition coefficient for THC from a buffered solution. The new organic solvent/plasma partition coefficient should permit the calculation of unbound THC and thus the plasma binding of nonpartitionable material. Although a theoretically feasible procedure, we realized that the organic solvent would denature the protein in plasma so that it could not bind THC. Only if we had a solvent or phase that did not denature protein in plasma, and into which THC could partition, could the problem be solved. But what are other potential phases? Is there anything normally in contact with plasma protein that could reversibly extract or partition substrates from plasma? Red blood cells certainly do not denature plasma proteins and do partition drugs with plasma water. Using these erythrocytes as a partitioning phase permitted the determination of the protein binding of THC as 98 percent with minimum variability. [18] The procedure also provided the rapid determination of plasma protein binding for

drugs such as herion that are tooo unstable to be determined by 8 to 20 hours of ultrafiltration and equilibrium dialysis.[19]

Inherent in the above data is information that could solve another problem. THC has low aqueous solubility (1 mg/L). To study its pharmacokinetics, it had to be administered to animals in amounts that would well exceed its solubility. Could one prepare a true aqueous solution or preparation that could readily distribute into the systemic circulation? The problem was solved simply by relating the goal with the available information. Blood was withdrawn from the animal, the necessary does of THC readily dissolved in blood, and the blood was reinjected into the animal, since with 98 percent protein binding, the solubility of THC in plasma is 50 times the 1mg/L of water.[20]

It was claimed that female and male sex-carrying spermatozoa could be separated by electrophoresis. Our great plan was to take advantage of this phenomenon to give boys or girls, bulls or cows, on order. It was even projected that females could be innoculated by extracts of male or female sex-carrying sperm to be immunized against the bearing of one of the sexes. Since sexing chicks was an ancient art, I thought chicken procreation would be rapid enough to challenge the hypothesis. My veterinary friends admonished me that fowls were anomalous, that the x-y chromosomes were in the egg and not the sperm. Obviously, it would be difficult to separate bobbing eggs by electrophoresis. Since rabbits were obviously fecund, the next prospect was to separate rabbit sperm and artificially inseminate with the separated electrophoresed fractions. Rabbits only ovulate on coition so that a vasectomized buck had all the fun while other frustrated males, after exposure to passionate females, had to be satisfied with furlined, thermally-controlled test tubes. Surprisingly, the collection at one electrode gave significantly greater males in the litters. However, we monitored the sperm electrophoresis by cinematography. These pronographic movies showed that all spermatozoa were pulled back by their tails and the more vigorous swimmers moved more rapidly in the opposite direction. Control studies showed that you didn't need to electrophorese, that male-sex-carrying sperm were more viable than female-sex-carrying sperm, and that enhancement of males in the litters was merely a consequence of selective dying rates on sperm swimming in salt solutions. There was a serendipitous discovery: male births were favored by insemination days prior to ovulation where female-sex-carrying sperm are more apt to die or weaken waiting for the egg; insemination, at ovulation, evens the odds.

Pharmacokinetics is vital in modern clinical pharmacology where the time course of pharmacodynamic, pharmacological, and chemotherapeutic action is related to the time course of the drug in the living organism.[21-23] Thus, optimal dosage regimens can be prescribed for proper treatment of disease with accompanying minimum toxicities for individuals who differ pharmacogenetically, nutritionally, physiologically, or with disease states.

The good practicing physician of today should be, and of tomorrow must be, a practical phamacokineticist to take into account biological variability in drug utilization. At the 5th Chemotherapy Conference in Vienna in 1967[24] and in subsequent publications, I forecasted that individuals would be pharmacokinetically and metabolically characterized routinely and individualized dosage regimens would be the norm.[23, 25-30] My forecast at the conference that the individual could be montitored continuously and the values processed by a computer to adjust individualized dosage regimen, even by the general practitioner with a hand-held calculator, was greeted with skepticism. I was questioned as to when this would be effected and my prediction of "within ten years" was rewarded with a titter of laughter. Fortunately, for my ego, Paul Kuhne, the editor of the German Medical Tribune, came to my defense and, in a kind editorial projected that these statements were a true evaluation of the forthcoming reality of clinical practice.[31]

Present practices can be compared with these prognostications. Creatinine clearances are used for adjustments of dosage regimens in the renally insufficient. Amobarbital and antipyrene clearances are used as criteria for adjustment of doses in the hepatically inadequate. The World Health Organization has established pharmacokinetic tests of ratio of metabolites in the urine of tuburcular subjects to determine whether an individual is a fast or slow acylator of isoniazid, a drug whose elimination rates are racially differentiated.

Clinical pharmacokinetic laboratories are established in many of our hospitals where the ten to twelve drugs of critical potency-toxicity ratios, e.g., digoxin, phenytoin, and many antibiotics, are semi-routinely monitored to adjust specific dosage regimens. I personally have trained oncologists to use hand-held programmed calculators to predict blood levels on different rates and amounts of infusion of methotrexate and fluorouracil. The basic pharmacokinetic parameters had been obtained from an intravenous bolus of a subtherapeutic dose.

The great number of today's clincal pharmacology papers reflect the accepted responsibility of the pharmaceutical industry to provide rules for the adjustment of individualized dosage regimens based on quanitfiable variations in renal and hepatic clearances, with consideration of abnormalities due to disease, protein binding, nutritional status, and gastrointestinal absorption. The hand-held programmable calculator is used by the practicing physician to adjust dosage regimens pharmacokinetically at the bedside to maintain desired body levels for desired times.[17]

Some Controversial Conclusions

In summary, and to answer our questions, one can presume that all people have varying degrees of the potential for creativity, a potential that should be magnified by intelligence and can be used best with a background of factual knowledge and a broad information base. This potential is a function of the personality traits, individuality, and culture biases of the individual. Although they cannot be taught, an atmosphere can be established wherein one is exposed to the creative process. Examples are given that may be emulated. Individuals can be challenged to be innovative, stimulated to perform, and encouraged to be individualistic, to foster rather than stifle creativity.

Other than the requirement that intelligence benefits both the obtaining of good grades and demonstrating creativity, there is not necessarily a link between excellent grades and creativity. I have known many who can memorize reams and spit back the information, and who can subsititute into standard equations but are incapable of applying their knowledge to solving a problem dissociated from the routine of the classroom. Their horizons are certainly not broadened by the uncreative passivity of modern university testing, based on true-false and multiple choice examinations that do not foster logical patterns and innovative solutions

I recently watched a Japanese-American (on public television) discuss the effects of Japanese culture on their productivity and creativity. He pointed out that Japan has only four Nobel Prize winners, only one-tenth as many as the Dutch, who have one-tenth the population. A distinguished Japanese Nobel Prize winner wondered if Japan has the creativity necessary since it is throttled by the Japanese cultural patterns that promote cooperation and conformity and make a fetish of teamwork and not "rocking the boat." Certainly, Japan has competed successfully in the industrial world, but it was stated that their advances in the electronic, automobile, and other industries, as well as their attention to quality control, were based on innovations from the West. The narrator, of Japanese origin, admitted Japanese education is highly competitive and only the Rho Chi-like best are admitted to the universities. However, it was pointed out that the competitions were based on many memory

questions and the solving of tricky problems that in no way promoted creativity or challenged innovative capacity.

The minimization of laboratory courses in American pharmacy schools has forced the undergraduate student to accept the concepts and paradigms presented by textbook writers or nonresearch-trained instructors. He has no opportunity to evaluate his own experiments critically and to solve his own problems in the laboratory.

Many of you have asked about "The Beehive" and the bee in the lapel and asked for an explanation. It started when I appointed my first Florida post-doc, now a professor of pharmacy at Aston in England, to organize the laboratory coffee club where each contributed for all they could drink. The purpose was to enhance creativity by avoiding inefficient two-hour coffee breaks in the distant cafeteria. He put large signs over the lab door admonishing: "Beehive members, pay up!" The "Beehive" represented the industry and productivity that our group should maintain. Thus, when visitors came from afar, or coworkers left, we presented them with a diploma signifying that they were honorary members of the "Order of the Bee," that they were entitled to free coffee whenever they returned, that they were obligated to befriend all fellow members, that they had full right to argue at all times with the professor, and above all, to work hard and be a "Bee."

I found some lapel symbols that looked like bees (but were really flies) and distributed them with proper ceremony to co-authors when they had demonstrated their own individuality and creativity. We designed a more elegant lapel bee, made of 18 karat gold, with ruby eyes and seed pearls on the wings, which a Taiwanese post-doc contracted for us in Taiwan. At first, he reported that the jeweler could find no seed pearls and we wrote him that we would do without them. Before he received our letter, he wrote that all was well, that seed perals had been found in the Chinese apothecary where they are ground and used for stomach ailments, a sort of expensive antacid. Thus, what you see on the wings of our bees, around the world, are true medicaments and their finding was an exercise in serendipity.

What started as a joke became a serious matter of recognizing creativity. Distinguished colleagues from all over the world requested admission and we initiated an exalted membership. We have had the opportunity to give formal award ceremonies on special occasions in far away places; to the two grandfathers of pharmacokinetics — Torsten Teorell in Stockholm and Hartmut Dost on the occasion of his retirement celebration in Germany. Also inducted was Gerhard Levy in Jerusalem and Erich Gladtke, the initiator of pediatric pharmacokinetics at the special symposium of the Year of the Child.

There is an oath initiated by the Duchess of Maine in the 18th Century for her order of the Bee: "I swear by the bees of Mount Hymettus to always wear the symbol of the order of the bee and to always practice its principles. If I do not do this, may honey turn for me into gall, flowers into nettles, wax into tallow, and may I be stung by wasps and hornets."[32]

Summary

Finally, and what may be a fitting end for this recounting, there is a quotation of Francis Bacon's that gives a poetic interpretation of creativity in the scientist: "A scientist is neither an 'ant,' storing what it finds lying about ready-made, nor a 'spider,' spinning a web out of what its entrails secrete. He is a bee, visiting innumerable flowers and collecting the nectar it finds in them; but storing not this nectar in its crude state but the honey into which it turns."[33]

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