THE PHYSIOLOGIST

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Cover: Janet Howell Clark, p. 397.

Editorial

"The Lady Doth Protest Too Much, Methinks"
(Hamlet, Act III, Scene ii, Line 256)

Once again the actions of the Animal Liberation Front (ALF) have resulted in the termination of Federal support for a leading biomedical research institution. The City of Hope Medical Center, like a number of other institutions violated by ALF terrorists, has been found guilty as the perpetrator of a crime, rather than the victim of one. The termination of NIH support for the City of Hope Medical Center raises questions about the ability of researchers within the scientific community to monitor activities within their own institutions.

Since 1953, physiologists and other biomedical investigators have abided by the APS "Guiding Principles in the Care and Use of Animals" and more recently the PHS "Policy on Humane Care and Use of Laboratory Animals." In most cases, the problems uncovered by ALF and other antivivisectionist groups cannot be attributed solely to experimental procedures. Instead, a number of problems appear to be associated with the institutions' animal care facilities, which come under the jurisdiction of the Agriculture Department's Animal and Plant Health Inspection Service.

We must realize that with the termination of funding at the University of Pennsylvania and the City of Hope, and therefore the confirmation of misdeeds claimed by ALF, the activities of radical animal rights groups are likely to intensify. Our response to these raids cannot be to cry foul and claim that we are guiltless, since the recent successes of the animal welfare groups have resulted in their taking the higher moral ground. In many cases, the public, as well as Federal and State legislators, have forgiven them for their criminal activities because they have uncovered the misdeeds of the biomedical community.

The time has come to launch an offensive of our own against these ALF aggressors. We must strive to convince the public, which benefits from biomedical research, that experiments with animals have indeed greatly advanced the frontiers of medicine over the years. In addition, we must work within our own institutions to ensure that facilities used are adequate for the proper care of animals and that animals used in experimentation are not subjected to unnecessary pain, suffering, and inhumane treatment.

It is imperative for the biomedical community to emphasize and dramatize that its house is in order so that ALF's next raid is judged as a criminal violation and not the liberation of abused animals. The next time we cry foul, we cannot allow the animal rights groups to respond "The lady doth protest too much, methinks."

Martin Frank
Executive Secretary-Treasurer

Caroline tum Suden Award

Caroline tum Suden Professional Opportunity Awards of the American Physiological Society will be granted to as many as six graduates or postdoctoral fellows who present a contributed paper at the 1986 FASEB meeting. This award provides $500, a complementary registration at the meeting, and a waiver of placement service fees. Male or female students or fellows in any area of physiology are eligible. Please check the box on the APS abstract form for student prize.

APS/Gastrointestinal Section Student Research Awards

The Gastrointestinal Section of the American Physiological Society has initiated an awards program to challenge and reward students and postdoctoral fellows who are concentrating their efforts in gastrointestinal research.

Two awards will be made annually at the APS Spring (FASEB) meeting beginning in 1986. One award will be given for work done while enrolled as a student for a doctoral degree. The second award will be given for work performed during the first three postdoctoral years. Each award will be for $300; $100 as an honorarium and $200 to defray the expense of attending the meeting.

Applicants must send a copy of their abstract that will be presented at the Spring meeting and a complete application form to Dr. Herbert Ormsbee, SKF Laboratories, 1500 Spring Garden St., P.O. Box 7929, Philadelphia, PA 19101. Applications must be postmarked on or before January 15, 1986. All members of the GI section of APS will be receiving an application form; nonmembers can obtain a form upon request to Dr. Ormsbee.

The abstracts will be ranked by the members of the GI Section Steering Committee. The winners will be notified in early March 1986, and presentation of the awards will be made at the annual meeting of the GI Section during the FASEB meeting.

XXX International Congress of Physiological Sciences
July 13 - 18, 1986 Vancouver, Canada

The XXX Congress of the International Union of Physiological Sciences will take place at the University of British Columbia, Vancouver, British Columbia, Canada, from Sunday July 13 to Friday July 18, 1986. The University of British Columbia, with views of sea and mountain, boasts one of the most beautiful campuses in the world. Ten kilometers from the heart of downtown Vancouver, the university lies secluded on 450 wooded hectares. UBC is reached via both private and public transportation. All participants, including invited lecturers and symposia participants, must register.

Deadline dates: receipt of abstract and registration fee, Dec. 1, 1985; withdrawal of abstract, Apr. 1, 1986; application for accommodation, Dec. 1, 1985. *Information*: J. R. Ledsome, University of British Columbia, Vancouver, BC V6T 1W5, Canada.

The Language of Polypeptides and the Wisdom of the Body

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For the title of this lecture I have purposely included the words which we all associate with Walter B. Cannon's memorable 1932 book, *The Wisdom of the Body* (4). Probably few of us know that this choice of words did not originate with Walter Cannon. In the preface for the first edition, Cannon wrote: "In 1923, the late Professor E. H. Starling, of University College, London, gave the Harveian Oration before the Royal College of Physicians. . . . His oration he entitled *The Wisdom of the Body.* 'Only by understanding the wisdom of the body,' he declared, 'shall we attain that mastery of disease and pain which will enable us to relieve the burden of mankind.'" Then Cannon went on to say, "Because my own convictions coincide with those of Professor Starling, and because the facts and interpretations which I shall offer in this book illustrate his point of view, I have chosen to give the title of his oration to the present volume." A gracious statement on the part of Cannon, but also what a propitious choice of words, on the part of Starling, to describe the goals and hopes of all of us physiologists! This title, *The Language of Polypeptides and the Wisdom of the Body,* I have chosen because my own life and my own laboratory have been devoted over the years largely to the study of polypeptides in the brain. The picture I am going to present here, while centered on the physiology of the polypeptides in the brain, will rapidly enlarge to become a far wider view of the existence and significance of these polypeptides throughout the body.

In the days of Walter Cannon, physiologists viewed the nervous system as fundamentally electrical in its reductionist mechanisms of action. The concept of a neurohumoral mechanism involved in synaptic transmission was only just emerging through the work of Otto Loewi and Henry Dale, along with Cannon's own research. The molecules that were considered candidates for playing a role in this neurohumoral transmission were few in number and small in molecular weight. Along with acetylcholine, the sympathin studied and so named by Cannon was among the few molecules considered probably to be neurotransmitters; it was later identified by von Euler as norepinephrine.

The Walter B. Cannon Memorial Lecture sponsored by the Grass Foundation was presented at the 1985 FASEB Spring Meeting, Anaheim, CA. The text was edited by K. Klivington, Ph.D., of the Salk Institute, from a recording of the lecture as delivered. The author expresses his sincere appreciation of Dr. Klivington's efforts in preparing this summary.

The relatively simple picture was to change dramatically over the last 15 years. There are now close to one hundred known brain peptides. Some have been characterized chemically; others have been identified by reliable, highly specific radioimmunological methods. Most have biological activity in various parts of the brain as will be described here. If our current knowledge of brain peptides dates back only about 10 or 15 years, the idea that neurons might produce proteins or peptides in some functional way is actually considerably older. Much of the credit for realizing this possibility is due to the early morphologists, particularly to Ernst and Berta Scharrer; they observed that neurons, in invertebrates as well as in vertebrates, either show in permanence or have cycles of appearance and disappearance of histological formations in a pattern that morphologists had always associated with the secretion of proteins in other (non-neuronal) cells, particularly endocrine cells such as those of the thyroid or of the pituitary gland.

In a famous text for the Meeting of the Association for Research in Nervous and Mental Disease in New York in 1939 (20), the Scharrers presented the observations of what led them to the concept of neurosecretion. While their original work and that of other experimentalists in Europe (the German school with Spatz and Bargman, the French school with Roussy and Mossinger, Colin and Stutinsky) dealt primarily with the "secretory appearances" of neurons of the supraoptic and paraventricular nuclei, the Scharrers proposed that the concept of neurosecretion might apply to neurons in locations other than the hypothalamus. From observations in invertebrates, the Scharrers even anticipated some of the current proposals that in the early phylogeny it is difficult to differentiate nerve cells from secretory cells.

The discussion and conclusions that follow derive largely from the efforts of a few people to pursue and investigate a proposal of John Green and Geoffrey Harris, in the late 40's, to explain the mechanisms of

Roger Guillemin

hypothalamic control of the adenopituitary functions. This quest for the solution to a rather narrowly defined question provided answers of far wider significance. Green and Harris (9) had proposed that molecules manufactured by certain neurons in the hypothalamus (as per the neurosecretion of the Scharrers) would flow through a peculiar system of portal vessels extending from the ventral hypothalamus to the anterior lobe of the pituitary gland. There these molecules would provide the information necessary for the physiological regulation of the secretion of the pituitary hormones. This rather novel proposal was the only alternative for a pathway of hypothalamic-pituitary relationships that could not be exclusively built of neurons and nerve fibers, since morphologists had concluded to the total absence of nerve fibers in the parenchyma of the adenohypophysis. The routes that led eventually to the proof of this concept were complex and filled with false leads. One of the original proposals leading eventually to the isolation of the postulated molecules from the hypothalamus was the idea of studying these interrelationships between the hypothalamus and the pituitary with in vitro methods.

In the first paper that I published in this field in 1955, I described a study of pituitary secretion in classic tissue cultures, using the method of Alexic Carrel as taught to me by Pomerat in Galveston. Pomerat and his students showed that pituitary cells can survive, grow, and even differentiate for weeks and months in vitro but would eventually lose their secretory ability completely as shown when their culture fluids were tested in the mouse pregnancy test, a simple bioassay for gonadotropins. In my study, I showed that, in pituitary tissues cultured alone, the secretion of adrenocorticotropin (ACTH) (for which assays were more sensitive than for gonadotropins) dropped to zero by day 8. It was possible, however, to start the secretion of ACTH again if these fragments of the pituitary were cocultured with a fragment of the ventral hypothalamus. To put it simply, this result said that something produced and released by cells in these fragments of hypothalamus could stimulate the nonfunctional pituitary cells again to secrete ACTH. A simpler method based on short-term incubation was also established about the same time by Murray Saffran at McGill University in Montreal; it led to the same conclusion.

It was not until 1968, however, that with Roger Burgus, Dominick Desiderio, Thomas Dunn, and Wylie Vale, in my laboratory in the Department of Physiology at the Baylor College of Medicine in Houston, we first discovered the structure of one of these hypothalamic peptides. We had isolated the thyrotropin-releasing factor; once characterized by mass spectrometry it turned out to be a rather unusual tripeptide. From the work of several laboratories it is now known that there is one hypothalamic peptide responsible for the secretion of each of the pituitary hormones (see for reviews, Refs. 7 and 19); these peptides are the *releasing factors*. There is also a *release-inhibiting* factor, somatostatin, which, in various circumstances, inhibits the secretion of growth hormone and thyrotropin. The structures of all these molecules involved in control of the secretion of the gonadotropins, ACTH, β-endorphin, thyrotropin, prolactin, and growth hormone have been established for several animal species and some are shown in Figure 1.

Examination of our current knowledge of the language of peptides reveals the lack of an essential key to that language. It is the case in 1985 that when the structure of any peptide is presented to a peptide chemist, he has no way of knowing whether it is a hypothalamic releasing factor for corticotropin or a releasing factor for growth hormone. There are no obvious relationships that have been found between the primary structure of any of these peptides and their biological activity. A chemist well versed in the many published reports of the primary structures of biologically active peptides may recognize certain general characteristics such as a family resemblance between glucagon and growth hormone-releasing factor or among dynorphins, enkephalins, and endorphins. However, a relationship between structure and function for biologically active peptides is never obvious, and it is of little heuristic significance to say that this is so because we know so little of the structure of the pertinent receptors. Relating a given primary structure to a particular biological function remains a process of empiricism. It is because of this that when isolation of a novel peptide is attempted, the bioassay on which the isolation process is based must be absolutely specific.

Peptides can be recognized by radioimmunoassay techniques and visualized in the cells that produce them by immunocytochemical methods. Neurons can be stained, for example, specifically for the peptide LRF, the gonadotropin-releasing factor. Other neurons stain specifically for the growth hormone-releasing factor, others for the corticotropin-releasing factor, and others for enkephalins, endorphins, neurotensin, and so forth. The morphologist can work out a complete map for the distribution of each kind of peptide-containing neuron in the brain and spinal cord. Fitting the patterns together has led to remarkable observations the sig-

TRF (thyrotropin and prolactin releasing factor): pGlu-His-Pro-NH_2

LRF (gonadotropins - LH and FSH releasing factor): pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2

oCRF (corticotropin and ß-endorphin releasing factor): Ser-Gln-Glu-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Met-Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Ala-His-Ser-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-NH_2

bGRF (growth hormone-releasing factor): Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Asn-Arg-Gln-Gln-Gly-Glu-Arg-Asn-Gln-Glu-Gln-Gly-Ala-Lys-Val-Arg-Leu-NH_2

Somatostatin (inhibitor of the secretion of pituitary growth hormone, insulin, glucagon and some other peptides): H-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

Figure 1
Primary structures of hypothalamic hypophysiotropic peptides (o and b designate ovine and bovine, respectively).

nificance of which is not obvious, however. In a recent review (16), Palkovits mapped the reported distribution of peptides throughout the brain, showing that particular peptides are not confined to specific regions but are instead widely distributed in patterns which have no known or obvious functional correlations. In the paraventricular nucleus of the hypothalamus he found as many as 21 different peptides in cell bodies and 30 in nerve terminals. "This," he comments, "is the highest number of neuropeptides present in a particular brain nucleus within the central nervous system." In addition, he confirms the now well-recognized fact that there are several instances in which two different peptides are present in the same neuron within this nucleus. There have been reports of more than two peptides in a single neuron.

In one example of this process of generalization, Petrusz from Chapel Hill showed some time ago by immunocytochemistry that somatostatin is ubiquitous throughout the brain, though with a unique distribution. There is no unifying concept about what somatostatin does in all the different brain locations, but it is no longer possible to consider it a purely hypothalamic peptide, the source from which we isolated it. Indeed, the function of somatostatin in the cortex or the hippocampus has to be different from its hypophysiotropic role as hypothalamic somatostatin. The same dilemma exists regarding the function of extrahypothalamic LRF (gonadotropin-releasing factor), CRF (corticotropin-releasing factor), or TRF (thyrotropin-releasing factor). The situation is becoming even more complex, and indeed more interesting, as recent discoveries show: Charlie Gale, in the Department of Physiology at the University of Washington in Seattle, Donna Koerker, and their collaborators were the first to observe that somatostatin injected in the baboon centrally or peripherally inhibits the secretion of growth hormone, as we had said it does in the rat, but also that it produces a dramatic drop in blood glucose concentration. Eventually it was recognized that somatostatin is an inhibitor of the acute secretion of insulin and glucagon (7). Simple calculations showed that it was impossible for the amounts of somatostatin measured in the hypothalamus, when diluted in the peripheral blood, to modify the secretion of insulin and glucagon at the islet level. It was, however, soon recognized by two groups, Dubois in France and Luft and Hökfelt in Stockholm, that there is a peripheral source of somatostatin in the delta cells of the pancreas (7).

It soon became evident that these discoveries marked the beginning of a new era in peptide research. The original hypothalamic peptide, which acted at the level of the pituitary, was now found throughout the brain and also in specific cells of the endocrine pancreas. This was the observation that finally led to the complete change in the notion of tissue specificity of these (originally) so-called brain peptides or gastrointestinal (GI) peptides. All the peptides originally isolated in the brain have been found in the gut or in the pancreas, and vice versa. Historically, the biological activity corresponding to substance P had originally been found by Gaddum and von Euler in extracts of both the gut and the brain, but it was not until much later that Susan Leeman and Rolf Studer showed that it is indeed the same molecule in the gut and in the brain. The distribution of substance P is unique and different from that of TRF, somatostatin, LRF, CRF, and other molecules such as cholecystokinin (CCK). Fragments of CCK and gastrin are to be found, again with their own distribution, throughout the brain.

What specific functions all these peptides have in the brain is still not known.

Is there a concept that can help design experiments that would be heuristic in helping to understand why peptides are in both the brain and the GI tract? The best known is in the APUD[1] concept of Tony Pearse (17) in London, proposing that all these cells containing and most likely utilizing peptides are derived from the neural crest: during the ontogeny, cells of the neural crest will migrate into the adrenal medulla and constitute the C-cells of the thyroid (known to secrete neurotensin and calcitonin) and the ganglia of the autonomic nervous system. These cells, being of neural crest origin, will thus be able to make primary amines and peptides. This APUD concept as originally proposed by Pearse was accepted for many years. It is no longer possible, however, to accept it as such. Nicole Le Douarin and her collaborators at the Institute of Embryology in Paris have been making grafts of the neural crest from quail embryos into the same age embryo of the chick; because of the presence of an unmistakable chromatin marker in the cells of quail origin, it is possible to trace the species origin of the various cells and follow their migration; the neural crest is indeed a temporary formation from which cells move to other parts of the organism during embryological development. They concluded that the neural crest is the origin of the C-cells of the thyroid, the chromaffin cells of the adrenal medulla, and some cells of the carotid bodies and also of the autonomic ganglia as well as the nerve plexuses of the gut. But the peptide- and catecholamine-secreting cells of the gut were not found to be of neural crest origin (11). Neither Pearse nor Le Douarin has apparently come up with a satisfactory proposal for the embryologic origin of these peptide-secreting cells of the GI tract. The nerve cells of the gut, particularly the acetylcholine-secreting cells in the myenteric plexus, do come from the neural crest. But these neurons are not the same as the peptide-secreting cells. However, the peptide molecules are the same in the GI tract and in the brain, as well as in other tissues such as the lung and the skin, where several have recently been characterized; their molecular structures have proved to be identical. The peptides, either in the GI tract or in the brain, are all parts of "families" of related precursors and mature peptides. For instance, hypothalamic growth hormone-releasing factor (GRF) shares extensive homologies with several peptides of GI tract origin, such as vasoactive intestinal peptide (VIP), glucagon, the PHI (Phe,His,intestinal) peptide of Mutt, and secretin (8). In this case, the homologies are essentially in the N-terminal part of the molecules; we can thus hypothesize that that part of the molecule is probably of more ancient origin than the C-terminal region. In fact, it is possible to do away with the last 15 C-terminal residues of GRF and maintain most of its potency (specific activity), and certainly all of its intrinsic activity as a releaser of growth hormone. This is one example of how families of peptides have now been recognized between the GI tract and the brain.

The peptides of concern here are well conserved across species. Figure 2 shows a series of sequences of all growth

[1]Amine content and/or amine precursor uptake decarboxylation.

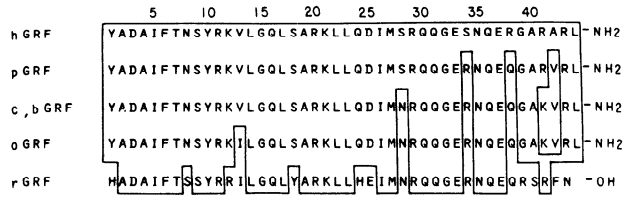

Figure 2

Primary structure of hypothalamic growth hormone-releasing factor of several mammalian species (h, p, c, b, o, and r designate human, porcine, caprine, bovine, ovine, and rat, respectively).

hormone-releasing factors that we have isolated and characterized in our laboratory at the Salk Institute from extracts of hypothalamic tissues. We first isolated the human form from a rare pancreatic tumor that caused acromegaly in a patient. The porcine sequence has only three substitutions. The goat and the bovine sequences have five substitutions. The one which differs most from the human sequence is the rat sequence, originally established by Spiess, Rivier, and Vale (21), also at the Salk Institute. The genes for both human GRF and rat GRF have been cloned. We know that the gene for rat GRF is relatively different in structure from the others, but between species all of these peptides with a given biological activity are very closely related. This also explains why the biological activity, i.e., release of growth hormone, is not species specific for these various forms of GRF (and in general the same statement can be made for all biologically active peptides). However, rat GRF has been shown to be two or three times more potent than any other species of GRF when tested in rat pituitary cells. Interestingly enough, all these forms of GRF are practically equipotent when tested in vivo.

When, in 1975, Hans Kosterlitz and John Hughes and their collaborators reported their structure of the enkephalins, and when, in collaboration with Roger Burgus and Nicholas Ling, we first established the structure of α-endorphin, both groups recognized that they were dealing with fragments of the C-terminal region of the β-lipotropin (LPH) molecule (review in Ref. 7). This molecule had been isolated by C. H. Li 10 years earlier, but no one had demonstrated any evident physiological function for it. Both groups proposed that these opioid peptides were most likely biosynthetic fragments of β-LPH. There was, however, a form of the enkephalin with leucine in the fifth position that created a problem. A form of β-LPH with leucine instead of methionine in position 66 had never been seen. So what was the precursor of Leu^5-enkephalin?

When, in collaboration with Floyd Bloom, we started mapping the endorphin-containing neurons and studying their physiology, we made two observations that began to resolve this doubt. With a highly specific antiserum, we found only a few endorphin-containing neurons located principally in the ventral hypothalamus in rat brain. We also recognized that these neurons have extremely long processes: we could trace some fibers with endorphin-positive nodes and terminals all the way to the periaqueductal grey. This pattern was reminiscent to Floyd Bloom of the type of network that he knew well for the norepinephrine-containing neurons found in his work on the locus coeruleus. But when this pattern of endorphin-containing neurons was compared to the results of Miller, Hökfelt, and Snyder, who had mapped enkephalin-containing neurons (the smaller pentapeptides with opioid activity), we observed that there was no relationship between the anatomical mapping of the endorphin-containing neurons and that of the enkephalin-containing neurons. Enkephalin-containing neurons are ubiquitous, though with a particular mapping both in the brain and in the spinal cord, and are also found in the adrenal medulla. Thus their distribution is totally different from that of the endorphin-containing neurons. In the paper that we published on the subject (1), we concluded that these observations had to mean that the endorphins and enkephalins must come from different precursors and were most likely the products of different genes. It is now known that the endorphins do indeed come from the β-LPH precursor, which is a common precursor also for ACTH and the melanotropins. From the original molecular biology work of Numa and collaborators in Kyoto, the complete precursor for these molecules is known (14). The structure of the precursor for the enkephalins was also established by molecular biology techniques by the groups of Udenfriend and Herbert in this country and again by Numa and collaborators in Japan (5, 6, 15): it was then recognized that it is totally different from that for β-LPH and the endorphins. The enkephalin precursor contains repeats of the sequence for Met^5-enkephalin and the Leu^5-enkephalin sequence in the ratio of 5 or 7 to 1, about what had been seen in the extracts of the brain both by the group of Hughes and later by Snyder.

The genes for the endorphins, enkephalins, and dynorphins have now been cloned and found to be different. There is thus a multiplicity of these peptides of different biogenetic origin with different mapping, and there are receptors involved that are specific for each of these various peptides.

There are also known peptides in the brain or in the GI tract for which no function has been determined. When the precursor for GRF was characterized in collaboration with the group at the Roche Institute, we recognized (10) that there is a C-terminal peptide following the GRF sequence that could easily be cleaved from the precursor and that it could be a secretory product of the neurons making GRF. Nicholas Ling synthesized this peptide in our laboratory, and we subsequently found that the native molecule is actually present in the GRF-containing extract and is protected both at the N-terminal and at the C-terminal. The peptide was isolated not only from the extract of the original tumor from which we isolated GRF but also from the hypothalamus of the human brain. No biological activity has been identified with it so far. I have offered to make our synthetic replicate of this molecule available to any colleagues who would have a rationale to test it in their own laboratory.

Another set of observations that must be taken into account in characterizing new peptides in the brain is the recently recognized possibility of alternate splicing of messenger RNA. Several examples of this process are known. I will mention here only the remarkable work of the group of Rosenfeld in San Diego that led to the discovery of alternate splicing of the messenger RNA which may result in either calcitonin in the thyroid or an entirely different peptide called calcitonin-gene-related peptide (CGRP) when the message is expressed in the brain (18). What is also remarkable is that this new peptide has a mapping of its own which is different from that observed for any other peptide. While its specific

function remains to be determined, there are some early observations that relate this peptide to control of blood pressure.

Peptides in the nervous system must either excite or inhibit the electrical activity of individual neurons. There is, however, no pattern to relate the structure of any of these peptides to their function. There is no way of knowing from their primary structure whether these peptides will either activate or inhibit any neuron onto which they are applied by microiontophoresis—another example of the general rule, or rather the state of the art, that I mentioned earlier. Enkephalins and endorphins were originally found to be primarily inhibitors of the electrical activity of neurons. We did, however, find an exception when, in collaboration with George Siggins and Floyd Bloom, we observed that both the enkephalins, and even more so the endorphins, when injected into the lateral ventricles of the rat brain, would actually stimulate the firing of neurons both in the brain stem and in the hippocampus, to the extent of producing epileptoid seizures in the hippocampus, as seen by electrocorticographic recording. The present explanation as proposed by George Siggins and collaborators is that the endorphins or the enkephalins inhibit some of the γ-aminobutyric acid-containing inhibitory neurons, which then release their inhibitory hold on hippocampal neurons.

Microgram injections of endorphins into the cisterna of the rat lead to a catatonic posture reminiscent of the catatonia in some types of schizophrenic patients (2). We proposed with Floyd Bloom that perhaps the endorphins are involved in some way in the control of normal behavior and that abnormality of these endorphins at the level of the hippocampus could be involved in some aspects of schizophrenia. The efforts of clinicians to date, however, whether using antagonists to opiates such as naltrexone or naloxone or using radioimmunoassays in various body fluids to approach this concept, have led to conflicting results.

What is unquestionable is that the endorphins and the enkephalins are involved in the physiological processing of pain. It is known that β-endorphin injected in spinal fluid is probably the most powerful analgesic agent available in clinical medicine. These diverse effects of peptides are clearly different from the limited roles originally proposed for them. The thyrotropin-releasing factor, for example, when injected in large quantities intravenously or directly into the ventricular fluid of the brain, has been shown to increase spontaneous motor activity, inhibit conditioned avoidance behavior, and oppose the effects of alcohol and other "tranquilizing" drugs. Thus the peptides have multiple and variable actions on many aspects of brain function which, in this particular case, have nothing to do with their hypophysiotropic activities.

Perhaps one of the most remarkable observations that has been made over the last few years is that there is some sort of "parsimony" in the use of the information encoded in a particular peptide, so that the same information may be used for identical ultimate purposes in and through different physiological systems. For instance, McCann and Moss in Dallas have shown (13) that the LRF molecule (originally characterized as the activator of the secretion of gonadotropins, which in turn stimulate the secretion of the gonadal steroids and maintain the germinal cells in the gonads involved as well as sexual life and behavior), when injected directly in the brain of animals that have been gonadectomized and hypophysectomized, will, in a matter of minutes, stimulate active sexual behavior, an effect clearly not mediated by the pituitary or gonads, which have been removed, but which is part of the overall normal sex response of the animal.

Another example of this same concept is the similar effects of CCK on hunger or satiety, whether it is injected directly into the brain or at the periphery. Recently, CRF, which in the brain leads to the secretion of ACTH and glucocorticoids, was found also to have true peripheral effects in elevating specifically secretion of norepinephrine at the level of the adrenal medulla and of some specific parts of the sympathetic peripheral system, all leading to the same ultimate biological organismic response to stress exposure (3). It is indeed one of the most intriguing observations regarding these biologically active peptides that they may, either at the periphery or within the brain, code sufficient information to initiate a complete, organized, physiological sort of response from the whole organism.

What has been known as "Dale's Principle" was essentially a formulation by John Eccles from the work of Henry Dale, saying "one neuron, one neurotransmitter." There is no doubt today that, in terms of peptides as putative neurotransmitters, one neuron may contain (and, we assume, utilize) more than one peptide over and above its containing one or another of the classic neurotransmitters (e.g., norepinephrine, acetylcholine, dopamine, and serotonin). This clearly indicates a need to revise Eccles's conclusion and leads to interesting possibilities. In recent work by Larry Swanson at the Salk Institute, for example, one can see by successive immunocytochemical reactions that the same neurons in the paraventricular nucleus of the hypothalamus of the rat contain arginine vasopressin, angiotensin II, and CRF. All three peptides can be shown to have a part of the integrated pituitary-adrenal response to stress. Moreover, one can modulate specifically and individually the appearance and the presence of any one of these three peptides by a combination of steroid pretreatment either acutely or chronically.

As noted earlier, there are close to 100 recognized peptides in the brain. It is now known that each neuron can actually modulate the expression of its genetic material for any one of these peptides in a manner which is still not understood. In the case of vasopressin and CRF, it is known, for instance, that the gene is controlled by glucocorticoids.

What is emerging from these findings is far more heuristic than Dale's "one neuron, one transmitter" theory. The neuron can now be seen as being able to secrete multiple peptides from separate genes, by alternate splicing of the same RNA, or by alternate cleavage of the same precursor. It is also known that in the same subcellular granule one can find one or other of the biogenic amines, along with some processing enzymes. Neurons are clearly a far more prolific system than Dale's concept suggests. There is an additional complexity in their capabilities. As a function of time, one can envision a neuron secreting only some fragments of a given precursor from its terminal, while at some later time secreting other fragments from the same precursor as well as processed products of another protein precursor. Once again, this shows the complex possibility of

information coming out from various terminals in neurons, both in the periphery and in the brain.

There is no unifying concept available to help determine what these many peptides might do in relation to the classic neurotransmitters. It is possible that the catecholamines, the biogenic amines, and/or acetylcholine affect the release of any one of the peptides in one way or another. Or it may be the other way round. Since there are so many of the peptides with different specific structures and so few of the "classic transmitters," I personally prefer the concept proposing that the neurotransmitters modulate the secretion or the release of the peptides. There is no solid evidence for this. Kosterlitz proposed several years ago that the enkephalins could work either as postsynaptic or presynaptic inhibitors or modulators of the release or reuptake of the classic transmitters.

Recently two novel possible roles at least for one peptide in the central nervous system have been proposed. VIP (vasoactive intestinal peptide, so named because it was first characterized in gut tissues) has been shown to be present exclusively in bipolar cells of layers III and IV of the (rat) cerebral cortex. This in itself is remarkable, since the other most prevalent peptides in the cortex (CCK, somatostatin, and CRF) have a heterogenous distribution when related to neuronal type. The location of these VIP-positive neurons in relation to the central arteriole of the cortical columns described by Mountcastle suggests that VIP released from some neuronal contact (dendrite?) in close proximity to the arteriole may produce vasodilation, thus modifying (increasing) blood flow in the whole columnar structure. It has also been shown that VIP, when added to the bathing fluid in physiological (nanomolar) concentrations, will produce glycogenolysis in mouse cortical slices. Indeed, VIP would work on neurons as it has been known to work on nonneuronal cells, i.e., increasing intracellular cyclic AMP, inducing phosphorylation of some cyclic AMP-dependent protein kinase that in turn can initiate glycogenolysis to glucose 1-phosphate, and inhibiting the synthesis of glycogen. This effect of VIP is similar to that of norepinephrine in the same assay systems. The novelty here is that VIP could be involved in local regulation of energy substrate for the neurons involved, whereas norepinephrine, due to its anatomical distribution in the neocortex, would be more diffusely involved, possibly acting simultaneously in multiple distinct regions of the brain (12).

The picture emerging from all this novel and accumulating knowledge is that of a central nervous system which, of course, possesses all of what the neuroanatomists and neurophysiologists have expressed in terms of anatomical structures and electrical functional relationships but which also looks like a gigantic multiendocrine organ secreting within itself or to very closely attached structures (the pituitary gland, the periventricular organs) a multiplicity of peptide molecules, most of them also known to be secreted by nonneuronal endocrine cells or tissues at the periphery (and thus not specifically neuropeptides). To return to our expression "the language of polypeptides," we have said that we do not really know the role(s) of these peptides in the brain. But we know quite well what many of these same peptides do at the periphery. So we have a local pituitary "dialect" for some peptides where they are hypophysiotropic, i.e., releasing or inhibiting the release of pituitary hormones. There is also a pancreatic "dialect" where some of the same molecules modify secretion of pancreatic hormones. But we do not know the brain "dialect(s)" when the same peptides are found in the neocortex, the hippocampus, the retina, and so forth. The biological significance of the message (the ligand) finally resides in the inherent postreceptor activation.

This information, in years to come, will undoubtedly bring us the answers to these many puzzles.

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Janet Howell Clark: Physiologist and Biophysicist (1889-1969)

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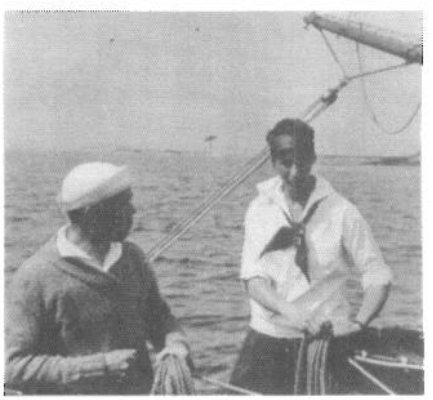
Janet Howell Clark, one of the earliest women members of the American Physiological Society, was remarkable for the range and breadth of her interests. Trained in physics, she worked briefly in astronomy before turning her attention to physiology and public health. Throughout, her scientific work was concerned with radiation and its effects on physiological processes; she became an expert on the impact of ultraviolet radiation on human health and disease. Her active career spanned the discovery of the effects of sunlight in preventing and curing childhood rickets, the recognition of the role of ultraviolet light in producing skin cancer, and growing awareness of the industrial damage and disease produced by radiation. Janet Howell was involved in research on each of these issues; she published 55 scientific papers[1] and a book, *Lighting in Relation to Public Health,* the first such text in the field (2). In her varied career, Janet Howell had served as a faculty member at Bryn Mawr College, Smith College, and the Johns Hopkins University, as headmistress of the Bryn Mawr School for Girls in Baltimore, and as dean of the Women's College at the University of Rochester. As a graduate student at Johns Hopkins, Janet Howell marched in women's suffrage parades in an effort to gain the vote. As one of the more distinguished American women in science, she later devoted much of her time and energy to improving educational and career opportunities for women and encouraging younger women to commit themselves to a future in scientific research.

Janet Howell was born in Baltimore on January 1, 1889, the eldest of three children. Her father, William Henry Howell, an eminent physiologist, was professor of physiology at the Johns Hopkins Medical School and later director of the Johns Hopkins School of Hygiene and Public Health. Janet Howell's mother, Anne Janet Tucker, born in Richmond, Virginia, was the daughter of one of General Lee's officers in the Civil War. Growing up in Baltimore, Janet was given the best possible education available to a girl of that period. She attended the Bryn Mawr School, founded in 1885 by a group of Quakers who believed that girls should have as good an education as their brothers. Under Miss Edith Hamilton, the girls were thoroughly schooled in the classics, especially Latin, Greek, and English literature. Although Janet initially considered applying to art school, she graduated at the top of her class in 1906 and thus won a coveted scholarship to Bryn Mawr College. The President of Bryn Mawr, M. Carey Thomas, was one of the four women who had raised the money to open the Johns Hopkins Medical School on the condition that women be admitted on the same basis as men. M. Carey Thomas and her faculty taught the young women students at Bryn Mawr to consider themselves fully as competent as men to undertake professional and scientific careers. The young Janet Howell was very much influenced by this attitude at Bryn Mawr and also by the personality of M. Carey Thomas herself. She decided to take advantage of the new opportunities to study science and mathematics and to major in physics.

Janet Howell graduated from Bryn Mawr in 1910 and went on to the Johns Hopkins University, where she received her Ph.D. in physics in 1913. Her dissertation, written under the guidance of J. S. Ames and A. J. Anderson, was a mathematical study of optical gratings, entitled *The Fundamental Law of the Grating* (10). This early study proved the high degree of accuracy with which the fundamental law of the grating held for the gratings then available for experimental work, and it also established Janet Howell's future interest in optical phenomena. After graduating, Howell spent two years as a lecturer in physics at Bryn Mawr College; one year, with a fellowship from the American Association of University Women, at Mt. Wilson Observatory in California; and one year as instructor in physics at Smith College. Her work was supported by a Huff Fellowship in 1913-14 and by a Sarah Berliner Fellowship in 1915-16.

In July 1917, Janet Howell married Admont Halsey Clark, an associate professor of pathology at the Johns Hopkins Medical School. In May 1918, they had



Janet Clark sailing with her husband in 1918.

[1]A complete bibliography of Janet Clark's papers, compiled by the authors, is available on file at the American Physiological Society, Bethesda, MD.

a daughter, Anne Janet. The couple spent one year together; in October 1918, Admont Clark died at the age of 30, a casualty of the great influenza epidemic then sweeping the country. As a young widow with a baby, Janet Clark moved in to live with her parents and soon started teaching in the Department of Physiological Hygiene at the Johns Hopkins School of Hygiene and Public Health. The School had just been opened and was admitting its first class of students. As Margaret Rossiter has noted in her extensive study of women scientists in America (12), the School of Hygiene was then second only to the women's colleges and Teachers College, Columbia, in offering positions to highly qualified women scientists. The women were given meager pay, but they did have time and facilities for research and the opportunity to contribute to newly developing fields and disciplines. Janet Clark was appointed instructor in physiological hygiene in 1918, assistant professor in 1920, and associate professor in 1923. She taught courses on the physiological effects of radiation, including visible and ultraviolet light, infrared radiation, and X-rays. Her courses on lighting included extensive discussion of the best lighting conditions for schools, factories, offices, and streets, and devoted considerable attention to the occupational diseases resulting from insufficient or excessive illumination—myopia, miners' nystagmus, and the high prevalence of cataracts among glassblowers, iron smelters, chain makers, and tinplate millmen. During this period, she became interested in the mechanism of production of cataracts, and much of her experimental work was devoted to showing that ultraviolet light precipitated lens proteins in the presence of salts and heat (see, for example, Refs. 3 and 5). In the laboratory, Janet Clark and her students studied the biological effects of different forms of radiation on a variety of simple organisms, proteins, and blood cells. They investigated the effects of radiation on nutrition, metabolism and growth, the possible influence of sunlight on resistance to infection, and the amounts of different forms of radiation required to kill pathogenic microorganisms. The discovery that sunlight could protect children against rickets stimulated a series of papers measuring ultraviolet radiation in sunlight and confirmed the idea that radiation could have healthful as well as harmful effects (for a concise summary of the research, see Ref. 4).

Janet Clark in the laboratory in 1925. (From the Alan Mason Chesney Archives of the Johns Hopkins Medical Institutions.)

Janet Clark continued her teaching and research on radiation at the School of Hygiene until 1935. Finding that there was no adequate textbook on the physiological effects of lighting, she wrote her own text in 1924; she continued to publish review articles on the state of the field as well as original research. In addition to her work on ultraviolet radiation, she published several articles on the X-ray diffraction patterns produced by muscles, bones, and tendons and on related physiological subjects. By 1923, Clark had already reached the highest position open to a woman at that time: that of associate professor at a major research institution. She continued at this rank for 12 years, gradually extending the scope and range of her research interests and developing an international reputation for her work on ultraviolet light.

In 1931, William Henry Howell retired as head of the Department of Physiological Hygiene. Since this had been one of the original and most important departments of the school, a national search for his replacement might have been expected. During the depression, however, the school's budget had been cut, and a faculty committee suggested that, to save money, "a man in his early thirties" be found to serve as acting head of the department until there were sufficient funds for a full professorship (7). The option of appointing Janet Clark as acting head of the department seems to have been unthinkable; the faculty committees clearly specified the need for a "suitable and available man" (8). When no such candidate could be identified, the Department of Physiological Hygiene was formally combined with Chemical Hygiene under the leadership of Elmer Verner McCollum. When Janet Clark resigned her position, physiological hygiene remained in the hands, if not under the formal authority, of another female faculty member, Anna Baetjer, who subsequently became nationally known for her research, teaching, and publications in the field of occupational health.

Janet Clark now accepted an appointment as headmistress of the Bryn Mawr School for Girls in Baltimore. At her first assembly, when she had the duty of giving out diplomas to the graduating students, the first in line was her daughter, Anne Janet. As headmistress, Janet Clark presided over the school's move from the center city to the countryside and maintained the institution's high academic standards during the difficult financial crisis of the depression years.

In 1938, Janet Clark left Bryn Mawr to become Dean of the Women's College and professor of biological sciences at the University of Rochester. The position appealed to her because it was not simply that of Dean of Women in a coeducational college: the men's and women's colleges were coordinate, each with its own campus, buildings, classrooms, and dormitories. The dean of the Women's College was therefore equal in rank to the dean of the Men's College and would be in a significant position to influence the quality of academic training for the women students. Alan Valentine, president of the University of Rochester, later explained why he had selected Janet Clark for the position: "I knew that she was not only the person of all persons that I wanted to have in charge of the Women's College at Rochester, but also a person I wanted to win as a personal friend. . . . In asking her about Chebeague (Maine) she spoke of running her motorboat alone from the Island to the mainland 'What do you do if it

Janet Clark and daughter, Anne Rodman, in their garden in Aberdeen.

stops running?' She replied casually . . . 'Oh, I'd fix it.' I said, 'You are the woman I have to have as Dean!'" (13).

At Rochester, Janet Clark devoted herself to curriculum reform and improved the academic environment for both faculty and students; she made many friends and was widely admired for her wisdom, warmth, and personal interest in the students. Appointed as professor of biological sciences, she taught biophysics to advanced students and continued research in her laboratory whenever time permitted. Under a grant from the Jane Coffin Childs Memorial Fund, she spent four years studying the effects of radiation and other environmental conditions on breast tumors in mice. Her good friend, Ethel Luce-Clausen, wrote of this period (11): "I know Janet Clark is a good Dean, but I would like to suggest that it is the creative spirit of the scientist that makes her one. She has the curiosity, the integrity that is needed for scientific research, the patience to try again when an experiment fails, the courage to abandon a cherished theory found to be untenable, and the pleasure in work for its own sake."

Janet Clark spent 14 very happy years at the University of Rochester. She was an integral part of the social life of the city and especially enjoyed the Wednesday Club, a group of ladies from social and university circles, who met each week for intellectual discussions and debate. Janet Clark's own speeches to the club were primarily on astronomy, a long-standing interest which she maintained throughout her career.

In 1952, a new president of the University of Rochester decided to merge the two Colleges into one coeducational college on the men's campus. Clark's position was to be downgraded to Dean of Women under the Dean of Men. Since this was not what she wanted, she decided to retire from administration and return to the School of Hygiene at Johns Hopkins where she could continue her research. At the time, she was 63 years old. She bought a house in Baltimore, lectured on environmental medicine, and for the next 15 years worked almost every day in her laboratory. She also enjoyed spending time with her family and three grandchildren.

Janet Clark continued to be active in organizations seeking to improve educational opportunities for women. She served on the board of directors of the new St. Paul School for Girls and the board of trustees of the Bryn Mawr School. She was actively involved in the American Association of University Women as a member of the board of directors and chairman of their international grants committee. She became chairman of the scholarship committee of the International Federation of University Women and befriended many of the young foreign students awarded fellowships to study in the United States. Janet Clark continued to attend international conferences in her field and served as a member of the photobiology committee of the division of biology and agriculture of the National Research Council. In addition to her membership in the American Physiological Society, she was a member of the American Physical Association, the Optical Society of America, and the American Association for the Advancement of Science. After a very active life, Janet Clark died suddenly of a heart attack on February 12, 1969, at the age of 80.

Janet Clark lived during a period when equal educational and professional opportunities for women in science were in their infancy. An earlier generation had fought hard for women's admission to the universities; in Clark's view, it was the responsibility of her generation to prove that the faith, hope, and ambition of that previous generation of women had not been in vain. She was pleased that her own generation had built on the struggles of the early pioneers in women's education, though she also wondered whether they had accomplished enough (Ref. 6 p. 2): "Quite honestly, I think the work that women are doing in the world today is interesting and impressive and becoming steadily more so. If in looking at it it does not seem as great as the dreams of the pioneers I think it should be remembered that it is easier to make a plan and to dream than to carry it out—to dream a dream than to make it reality. As you look at the women of the world today I think there is much that could fill the band of pioneers with enthusiasm and pride and that in the last two generations much has been accomplished." Janet Clark noted the major scientific contributions of women in mathematics, physics, biochemistry and astronomy and urged young women to undertake what she called the 'journey of research' (Ref. 6, p. 17): "And the stirrup-cup I would give to you who are starting on this journey is the promise that the road is full of unending variety, interest and adventure. You will need resourcefulness, ingenuity, perseverance, and faith in your own ideas, for there are pitfalls and mazes in the journey. The timid ones among you will spend your lives wandering around happily but footlessly in the first maze you strike but those with self-confidence, courage, and ingenuity will find endless enjoyment and satisfaction in working your way out of those mazes and in blazing new trails that are all your own."

Janet Clark with her three grandchildren in 1950.

Janet Clark devoted herself to this journey and to encouraging others along the path. She also lived a full life, rich with other interests and activities. She was an avid mountain climber and a seasoned sailor, sailing almost every day during the summers spent in Maine with her daughter. She found time for travel, for artistic interests and literary excursions; an amateur artist, she was known for her "lucious Reubenistic nudes" and, as an amateur poet, for her humorous verse (9). At a period when married women were considered insufficiently dedicated to pursue scientific careers and single women probably too neurotic to hold high positions, Janet Clark had achieved distinction both as a scientist and an administrator and did so with grace and style. As Ruth M. Adams, President of Wellesley College, wrote (1): "Not the least of the things she taught me was merriment and cheerfulness, how to have fun in the company of women as well as in the company of men, how to balance your life so that you could present at least a serene facade to people who depend on you in any fashion. It all adds up to Janet's life providing joy in this gift of strength and happiness."

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Recollections of 40 Years at the Worcester Foundation for Experimental Biology

In 1941 I received my Ph.D. degree under the direction of Sir John Hammond, F. R. S., and Dr. Arthur Walton at Cambridge University. Dr. Hammond's attitude toward research students was to leave them alone to sink or swim. He said that, "If a chap is going to be any good for research, he does not need spoon feeding." I took the same attitude. Most of my research associates or research students associated with the Worcester Foundation have good positions and are swimming very beautifully at present.

M. C. Chang (elected to APS membership in 1946).

In 1944, toward the end of World War II, I had planned to return to China but first wanted to spend a year in the United States. On a pleasant summer day, I wrote three letters to some US scientists. Two letters written to the agriculture department of a university were not answered, but Dr. G. Pincus offered me a fellowship at Clark University in Worcester, Massachusetts. Friends at Cambridge University and I were very excited because we thought that a fellowship in the USA was similar to a fellowship at Cambridge University, which amounts to having a lifetime income. I accepted a rather low salary to work on the transfer of cow eggs to other cows and perfusion of ovaries by a newly developed perfusion pump devised by Pincus and his associates. But I was more interested in learning the technique of in vitro fertilization of rabbit eggs, supposed to have been accomplished by Pincus in the 1930's.

I came to the Worcester Foundation for Experimental Biology in March 1945, some 40 years ago. The Foundation had recently been established by Drs. H. Hoagland and G. Pincus. It was still connected to Clark University at that time. When I arrived Pincus was in California, so I went to meet Dr. H. Hoagland at the state hospital where he was conducting studies on schizophrenia. When I got there, the people though I was a patient of Dr. Hoagland. He arranged for me to stay at the Y.M.C.A. for a few days. Later I moved to the Foundation where there was a lot of empty space and a nice apartment. I stayed at the Foundation as a night watchman for more than a year. In those days Dr. Pincus did not have a car, so we often waited for the bus together; he'd go back home, and I'd go to the Y.M.C.A.

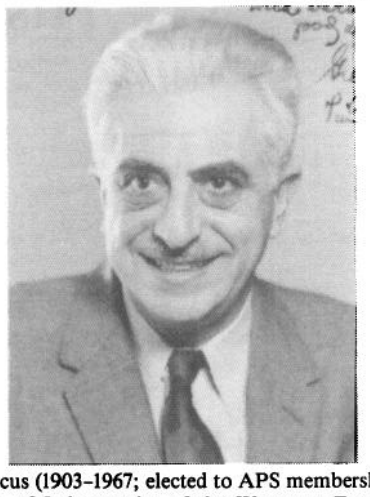
When I started fertilization studies in 1945, it was very interesting but not successful, including in vitro fertilization of rabbit eggs with Dr. Pincus. However, in 1947 I reported on the spermicidal effect of serum, noneffect of hyaluronidase on fertilizing capacity of sperm, and

the delivery of normal young after storage of fertilized rabbit eggs in my kitchen refrigerator and transferring them to other rabbits. Thus I was invited to give a paper by the UNESCO in Milano, Italy, in 1948. At the same time I also gave a paper at the First International Conference of Animal Reproduction and Artificial Insemination about the successful transplantation of eggs stored at low temperature. After submitting a paper in 1950 on fertilization of rabbit eggs to the American Sterility Society, they awarded me $1,000, which I used to buy my first car. When I told Dr. Pincus about this award, he was very pleased, since Dr. Oscar Hechter at the Foundation also received an award from the Endocrine Society. He said to Dr. Hoagland, "Why should we worry about money, our staff members could live on awards!" The capacitation of sperm in the female tract was reported in 1951, that may be the reason why the Ciba Foundation in London invited me to give a paper in 1952 and I had the chance to visit Denmark.

In 1951 Dr. Pincus and I started to work on the effects of various synthetic progestins on reproduction. This work led to the development, in 1959, of the oral contraceptive pill, which is still in use today. I understood that financially Dr. Pincus and the Foundation did not get anything, probably because Pincus was a consultant to the G. D. Searle Company. After Pincus's death in 1967, Dr. Hoagland wrote to the Searle Company suggesting that they give me some financial help. I also understood that the Searle Company asked him, "Who is M. C. Chang? Never heard of him." But in 1955, 1959, and 1967, the International Planned Parenthood Federation invited me to give papers in Tokyo, New Delhi, and Santiago. Because I had to spend a good deal of time testing all kinds of synthetic progestins for the oral contraceptive studies, I did not do much work on in vitro fertilization. When I reported producing young rabbits by transfer of eggs fertilized in vitro with in vivo capacitated sperm at the West Point meeting in 1959, they gave me a standing ovation at the final banquet dinner. In 1983, the International Society for Embryo Transfer gave me the Pioneer Award.

With Dr. G. Pincus' advice and encouragement, I received a Career Research Award from the National Institute of Child Health and Development (NICHD) in 1962. My highest salary with this award was no more than $25,000, but I am very grateful to the NICHD because they supported me until 1982. My first grants came from the Population Council in the 1950's and from the Atomic Energy Commission (AEC) to do some studies of irradiation of sperm and eggs. In those days, the AEC had plenty of money, but I only asked for $10,000 instead of $100,000. Later on, until 1984, my research was mainly supported by the NICHD, and I am grateful for their kind consideration.

From 1960 on, I did many diverse experiments, trying to cross hare and rabbits, minks and ferrets, transfer of eggs from one species to another, and other experiments mainly involving in vitro fertilization and attempting to find some more effective contraceptive agents. In 1963



Gregory Pincus (1903–1967; elected to APS membership in 1935) was Director of Laboratories of the Worcester Foundation for Experimental Biology from 1944 to 1956 and Research Director from 1956 to 1967.

Dr. Yanagimachi succeeded in fertilizing hamster eggs in vitro and reported the possibility of capacitation of sperm in vitro. In 1969 Dr. Stella Pickworth succeeded in fertilizing the Chinese hamster eggs in vitro, and Dr. Iwamatsu was able to fertilize mouse eggs in vitro by epididymal sperm. In 1973 and 1974 Drs. Miyamato and Toyoda succeeded in fertilizing rat eggs in vitro. In 1978 Drs. Hanoda, Fukuda, and Maddock succeeded in fertilizing deer mouse eggs in vitro. They did the work but I wrote the papers, so my name was on these reports.

Since the delivery of a normal girl in England in 1978 after transfer of in vitro fertilized human eggs by Drs. Edwards and Steptoe, the in vitro fertilization and transfer of human eggs for some sterility cases is practiced throughout the world. According to Dr. Yanagimachi, in vitro fertilization of human eggs is very easy because the capacitation of human sperm is very easy and takes a very short time. As we know now, capacitation of rabbit in vitro is very difficult to achieve. Possibly, if I had worked on human sperm, not rabbit sperm, the capacitation of sperm in vivo or in vitro might have been discovered much earlier than 1950.

In conclusion, I have had a very pleasant and comfortable life during the past 40 years at the Worcester Foundation, because the directors, my co-workers, the maintenance personnel, and other friends have all treated me kindly and nicely. I am a timid and peace-loving soul, who hates to fight and to grumble, and so I like to have a peaceful life, doing the things I like to do. During the past 40 years I was able to do just this and thus I have fulfilled my ambitions quite well. Recently Dr. Mark Mason asked me whether I have achieved what I had planned for my life. My answer was, "I achieved more than I wished for, so I should be very happy in my old age."

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Department History

History of Physiology at the University of Virginia

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Probably few universities anywhere were blessed during their critical initial years as was the University of Virginia with the determined and devoted services of an intelligent, enlightened, and politically influential founder such as Thomas Jefferson. His influence on higher education (and specifically physiology) in the state, while not exerted until the last years of his life, deserves more than a few words here. Besides ensuring that physiology would be taught at this university from the day of its founding, he was instrumental in procuring a teacher of the first quality, Robley Dunglison, whose influences extended for a decade or more beyond his tenure here. That these two founders briefly knew, respected, and influenced each other makes the story more interesting. The early establishment of our discipline in this university, its survival through a long period of handicap, and its later resurgence comprise the abbreviated history related below.

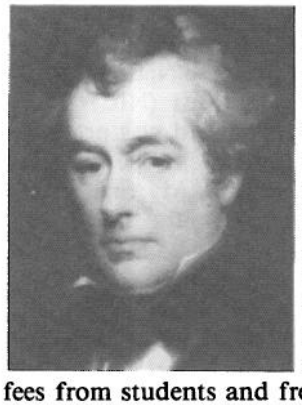
Jefferson's efforts to initiate higher education in Virginia had their roots in his conviction that education is essential to the survival of a democracy and that it should be provided to people of all social classes who are mentally capable of profiting by it. He led a group, also including James Madison and James Monroe, which succeeded in 1816 in chartering and raising the initial funding for "Central College" to be located near Charlottesville. In 1817 while the college was still little more than an idea, the state legislature, partially in response to Jefferson's influence, authorized the establishment of a state university, and Central College promptly offered its few assets. Jefferson fought off efforts to locate the university elsewhere in the state, and in 1819 the General Assembly chartered the "University of Virginia" to be located at Charlottesville. Jefferson was appointed Rector of the first Board of Visitors.

The Founding Period

The new Rector immediately started making and implementing plans. His foreign travels, extensive notes, and well-placed inquiries (including those to Joseph Priestly and Benjamin Rush) resulted in detailed ideas about how a university should be set up architecturally and administratively, and the Board of Visitors underwrote most of his ideas. He proposed eight professorships for eight "schools" of study. The professor in the School of Anatomy and Medicine was to teach "Anatomy, Surgery, the History of the Progress and Theories of Medicine, *Physiology,* Materia Medica and Pharmacy" [emphasis added]. No residence time was set for students. When a candidate had passed examinations on the basic courses in any one of the eight schools plus examinations in English and Latin, he would be awarded a certificate of graduation from that school. Jefferson also provided that the students should be self-governing and self-disciplining.

Bean (1) has summarized Jefferson's contributions to medical science in six areas, two of which are directly related to physiology. *1*) He encouraged the teaching of physiology as a major element in medical education. His catalogue of 3,113 books for the University Library included at least one on physiology, a textbook. *2*) He clearly stated the obligation of higher education in general to generate knowledge through research. In the words of Thomas P. Abernethy (History Professor at the University of Virginia during the 1930's) ". . . no early American save Mr. Jefferson would have dared to house a university in Roman temples, to employ a majority of foreign professors, to exclude the clergy and all their theologies."

The American pool of candidates for faculty positions was small. After a few appointments from that pool, Jefferson's expressed preference for recruiting in Europe to accepting second-class Americans prevailed,



and Francis Walker Gilmer, a lawyer and a friend of Jefferson's, was sent on a recruiting trip abroad. In London he met **Robley Dunglison,** a product of two years with preceptors, course attendance in Edinburgh, London, and Paris, and the University of Erlangen where he received the M.D. Dunglison accepted Gilmer's offer of a guaranteed salary of $1,500 per year plus course fees from students and free living quarters. For this he was to spend full time 10 months of the year teaching the subjects mentioned above. He was not to practice medicine on a regular basis but could consult.

After a difficult trip across the Atlantic, Dunglison and his new bride were met by Jefferson in Richmond and conducted to Charlottesville. The new university opened March 7, 1825, to 68 students, 20 of whom enrolled in Dunglison's "School."

Dunglison was an outstanding teacher, according to both the accounts of his contemporaries and his success in attracting students to his school, often as much as

one-third to one-fifth of the total university enrollment. In 1830 he influenced the Board of Visitors to offer Physiology as an elective available to students in the other schools of the university. Radbill (8) states that "Physiology was his special delight, and he considered himself a pioneer in the teaching of this subject in this country."

Other activities also received Dunglison's attention. In 1832 at the invitation of Dr. William Beaumont (after whom the headquarters building of our Society is named), he participated in the studies of Alexis St. Martin's gastric function. Beyond this collaborative effort there is no evidence that he did laboratory or clinical research. He was a very prolific writer all of his professional life, and in 1830 he wrote his textbook *Human Physiology* which went through seven editions, the last in 1856. He also published medical dictionaries and medical treatises.

Dunglison also carried on a limited, highly selective, medical practice. He accepted Jefferson's invitation to be his personal physician and attended him until Jefferson's death in 1826. He also treated James Madison, James Monroe, and Andrew Jackson (then President) and/or consulted with their physicians.

Jefferson and Dunglison are reported to have shown mutual respect from the day they met. Although he apparently accepted Dunglison's ministrations without question, Jefferson had a low regard for physicians in general based primarily on "... the adventurous physician [who] goes on, and substitutes presumption for knowledge...." He felt that the physician should actively intervene only as far as his firm knowledge supported him. Beyond that point his obligation was to observe and record the course of nature. Later in life Dunglison showed evidence of his exposure to this philosophy.

Dunglison finally resigned from his position at the end of the 1832-1833 term in order to accept an appointment at the College of Medicine of Maryland in Baltimore. The Board of Visitors acknowledged with thanks his outstanding contributions to the new university.

The Post-Dunglison Period

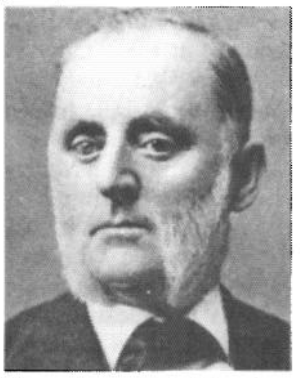
The next 8 years after 1833 were characterized by three incumbents with brief tenures who were apparently subsisting in Dunglison's shadow and trying to carry on as he would have. When academic questions arose, the Board of Visitors tended to consult Dunglison in Baltimore and later at the Jefferson Medical College of Philadelphia and to value his advice over that of the incumbents. Thus the Post-Dunglison designation seems appropriate for this period.

During this time the successive Professors of Physiology, Medicine, Obstetrics and Medical Jurisprudence were as follows: Dr. Alfred T. Magill (1833–37), Dr. R. E. Griffith (1837–39), and Dr. Henry Howard (1839–41). The annual university catalog of this period contained no course descriptions, and we can find no evidence that any of these professors were responsible for innovations. Apparently, they were not primarily physiologists, and they taught it solely as the handmaiden of medicine.

In the first annual catalog with course descriptions, that of 1842–43, Henry Howard's title had been changed to Professor of Medicine and Dr. Cabell, Professor of Anatomy and Surgery, began teaching Physiology.

The Cabell Period

Dr. **James Lawrence Cabell**[1] taught Physiology for 47 years, from 1842 until 1889. Prior to this he had been



Professor of Anatomy and Surgery for 5 years. The total of 52 years as a full professor in the same school possibly constitutes a record. Cabell's title was changed to Professor of Comparative Anatomy, Physiology and Surgery in 1849. During the seven years between 1842 and 1849 there was no faculty member with Physiology in his title.

Dr. Cabell obtained his Master's and M.D. degrees from the University of Virginia and pursued surgical studies and other medical training in Baltimore and Paris. He emphasized comparative studies (both in anatomy and physiology) throughout his career, which at the time was considered innovative. Among the textbooks that he assigned during his long teaching career were Dunglison's *Human Physiology,* Carpenter's *Human Physiology,* Carpenter's *General and Comparative Physiology,* Kirke and Paget's *Human Physiology,* Kirke's *Manual of Physiology,* and Gould and Agassiz's *Comparative Physiology.* The total school enrollment increased progressively during Cabell's tenure and his department usually received more than its share of the total. In the session for 1849–50 his department was the second largest next to Chemistry.

The intervention of the Civil War was perhaps the most influential factor during his incumbency. Both to ensure the survival of the institution and because of the increased need of the Commonwealth for educators and physicians, it was decided to keep the school intact and open during the war years. However, the enrollment dropped to approximately one-tenth of what it had been the last years before fighting began. By the end of the war the professors' annual salary had dropped to $1,757.72, in Confederate currency, which was worth $31.95 in gold. After the Civil War two faculty members (Socrates Maupin and John B. Minor) borrowed in their own names sufficient money from a Charlottesville bank for minimal restoration of buildings and facilities. As would be expected recovery was a slow process. It took approximately 35 years for the university's total enrollment to recover to its former level.

In 1862 the university buildings were converted into a military hospital and were frequently filled with the wounded from nearby battles. However, instructions continued and apparently Cabell taught physiology faithfully throughout the period. But his title included Surgery as well as Physiology, and he also gave generously of his time to treating the wounded. Cabell published several papers on clinical and public health topics, but the literature contains to evidence that he did laboratory research.

In 1868 the degree of Bachelor of Science was established, listing Physiology among its required courses. This was the first degree other than the M.D. to do so. However, starting in 1871 Physiology was no longer compulsory for the B.S.

[1]Photograph from Manuscripts Dept., Univ. of Virginia Library.

In 1889 Dr. Cabell retired at the age of 76 and died the same year.

The Barringer Period

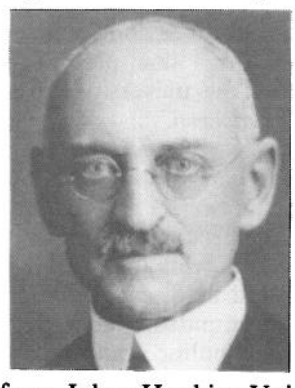
Dr. **Paul Brandon Barringer**[2] was appointed Adjunct Professor of Physiology and Surgery in 1889. One year later the "Adjunct" was dropped, and in 1893 his title was changed to Professor of Physiology and Materia Medica. Dr. Barringer received his M.A. and M.D. degrees from the University of Virginia. He then studied in various European medical centers, joined the faculty of Davidson College for 4 years, and came from there to the University of Virginia.

The annual catalog of 1889 makes the first mention of a Physiology Laboratory, but the description suggests that it was devoted largely to histology and pathology. Physiology lectures were directed primarily at the bearing of the subject on the subsequent study of Pathology and Therapeutics.

Barringer introduced the microscope for student use in this school. He wrote *An Abstract of Physiology for Medical Students* for use in his classes. His few publications do not suggest that he did laboratory research. During his tenure he was deeply involved in several important changes, e.g., residence requirements for the M.D. degree were changed from one year to two, three and finally four years; the University Hospital was built in stages, and about 1904 it became fully effective as a clinical teaching facility. Barringer retired from Physiology in 1906 after 18 years service.

The Pre-Modern Period

This period was initiated in 1907, when Barringer's title was changed to Professor of Therapeutics and Pharmacology and Dr. Theodore Hough was appointed Professor of Physiology with that subject as his sole responsibility. This period covered the incumbencies of Hough, Smith, Britton, and Anslow, all of whom regarded themselves primarily as physiologists with acknowledged, but secondary, obligations to medicine. They were devoted to research in varying degrees and apparently were prevented from creating a modern department solely by the inability of the university to support such a department at that time.



Dr. **Theodore Hough** was appointed Professor of Physiology in 1907. He received his A.B. and Ph.D. degrees from Johns Hopkins University and joined the faculty of Massachusetts Institute of Technology (1893–1903). In 1903 he accepted an appointment as Professor of Biology at Simmons College, Boston (1903–07).

During his first year at Virginia he had to spend most of his time on the construction and equipping of modern laboratories of physiology. The catalog for 1907 announced the opening of a laboratory for experimental physiology and that for 1908 announced the opening of a laboratory for elementary physiology. This permitted the announcement in 1909 of an advanced course in physiology for fourth-year students who wished to specialized in the discipline. Advanced Physiology (6 hours per week) took up in depth one area of physiology (varying from year to year). It provided ". . . an introduction to the methods of experimental investigation. . . " and each student did a research problem under the guidance of the professor. Professor Hough also announced a Physiological Journal Club with biweekly evening meetings which he conducted.

Hough published 34 papers. Topics that occurred two or more times included exercise physiology, muscle physiology, and the bearing of physiology on sanitation and hygiene. During his last three years he became Dean of Medicine and died in 1924.

Dr. Homer William Smith accepted appointment as Acting Professor of Physiology in 1925. The "Acting" was dropped from his title in 1928. Smith obtained his A.B. from the University of Denver in 1917, spent several years in the Chemical Warfare Branch of the Armed Forces, and obtained his D.Sc from Johns Hopkins in 1921. He came to Virginia after three years spent in the laboratory of Walter B. Cannon at Harvard Medical School.

Smith's brief tenure (1925–28) was not characterized by innovations in teaching but by a continuation without stint of the intense research program which characterized his whole career. The stories that his renal interests prompted him to follow along with a urine bucket behind camels and other exotic mammals in Charlottesville circus parades may be apocryphal. Some of his Virginia contemporaries suggested, only half in jest, that his later world renown as the founder of modern renal physiology followed naturally from his three-years' seasoning at Virginia. Smith left Virginia in 1928 for New York University where he spent the rest of his career.

Dr. **Sidney William Britton** accepted appointment as Professor of Physiology in 1928. Dr. Britton, an Englishman by birth, obtained his M.D. from McGill University in 1924 and spent two years as a Research Fellow at Harvard Medical School and two years as an Associate in Physiology at Johns Hopkins University.

An avid investigator throughout his career, Britton's research efforts were directed primarily toward adrenal physiology. His work demonstrated that the adrenal cortex contained one or more hormones which profoundly influenced carbohydrate storage and metabolism. He finally convinced a host of doubters who had believed that epinephrine from the medulla was responsible. A secondary theme to his research was comparative physiology with papers published on adrenal and other physiological processes in rats, dogs, cats, marmots, marsupials, sloths, reptiles, and a variety of monkeys. Late in his career, when World

[2]Photograph from Manuscripts Dept., Univ. of Virginia Library.

War II had started, he turned to the military-related topic of the physiological effects of acceleration, thus anticipating the strong modern interest in gravitational physiology prompted by man's exposure to the space environment.

Britton's principal teaching innovation was to initiate immediate efforts at recruiting graduate students. He was only modestly successful, probably because of the thin substratum of support for such activities at that time. However, the department gave its first masters degree in 1931 (a total of 5 during Britton's tenure) and its first Ph.D. in 1934 (a total of 2).

The tenured faculty in Physiology was expanded to two positions in 1929 and Dr. Edward Lyman Corey was appointed Assistant Professor of Physiology. Dr. Corey received his Ph.D. from Yale in 1928 and came to Virginia after one year as an Instructor at New York University. He was Professor of Physiology at his death in 1961.

Professor Corey's research complemented that of Professor Britton on adrenal physiology, although his publications show a variety of other research interests. The two appeared to work together during the war on the physiological effects of acceleration.

In 1950 the tenured faculty was expanded to three positions, and Dr. Grover C. Pitts was appointed Assistant Professor of Physiology. Dr. Pitts received his Ph.D. from Harvard in 1943 and spent 2 years as Research Assistant at the Harvard Fatigue Laboratory and 6 years on the staff of the Physiology Facility, Naval Medical Research Institute, Bethesda, Maryland, before coming to Virginia.

Pitts' research interests have involved the regulation of body composition and how it responds to exercise, obesity, hypergravity, weightlessness, and species differences.

Upon Britton's retirement in 1952 Dr. **William Parker Anslow** was appointed Professor of Physiology and chairman of the department. Dr. Anslow obtained his B.S. degree from the Massachusetts Institute of Technology and his Ph.D. from Cornell University. In 1944 he joined the faculty at New York University where he worked in renal physiology and became a protégé of Homer Smith.

Coming here, from the hub of the renal universe, Anslow was struck by our inadequate treatment of renal physiology, a distinction which we shared with most medical schools at the time. As the sections on renal physiology in available textbooks were woefully inadequate, Anslow wrote his own *Syllabus of Renal Physiology,* from which he taught. Later, at the request of the house staff he repeated the course for their benefit.

Research (particularly renal) also deeply concerned Professor Anslow. Although he pursued no program of his own, he placed great importance on encouraging and facilitating the development of research potential in others, both clinicians and graduate students. The department usually had one or more Research Associates and Research Fellows during his tenure and two M.S. degrees and one Ph.D. were awarded. The other two permanent positions were filled by Corey and Pitts. Assistant Professor Leonard Levine from Columbia was with the department for a few years after Corey's death.

During the incapacitation and eventual death in 1966 of Dr. Anslow and until the new chairman arrived, Pitts and Dr. J. Edwin Wood III served as Acting Chairmen. They were helped through this difficult period by teaching assistance from many considerate clinical colleagues.

The Modern Period

This period began in 1966 when Dean of Medicine Kenneth R. Crispell gave top priority to upgrading the five preclinical departments and was able to obtain a combination of federal and state funds to achieve this goal. During a period of several years his first objective of procuring five superior scientists-teachers to chair and rebuild the basic science departments was achieved. Each chairman was authorized to recruit a total faculty of 12. Next, funds procured by the Dean were used to construct a new medical education building, Jordan Hall, which was designed by the incoming chairman to meet the teaching and research needs of the faculty.

Dr. **Robert Matthew Berne** was appointed Charles Slaughter Professor of Physiology and chairman of the department in 1966. Dr. Berne obtained his M.D. degree from Harvard Medical School in 1943. After two years as a postdoctoral fellow under Carl J. Wiggers, Berne served for 16 years on the faculty of Case Western Reserve rising to professor before accepting the Virginia appointment.

Dr. Berne's research at Virginia has been directed at metabolic factors involved in the regulation of blood flow in the peripheral circulation, primarily in heart but also in brain and skeletal muscle. Adenosine emerged as the most promising candidate, and its role as mediator of metabolic vasodilation in various vascular beds as well as its other cardiac effects and its metabolism have been the primary frame of his research over the past 20 odd years. Berne's professional career has been punctuated with several national awards and honors for his research, teaching, and scientific and editorial services. He was President of the American Physiological Society in 1972.

The recruitment of a high-quality faculty of national and international reputation has continued to progress. The present faculty includes Professors Robert M. Berne, Brian R. Duling (microcirculation), John T. Hackett (neurophysiology and neuropharmacology), Howard C. Kutchai (membrane transport), Richard A. Murphy (biophysics and biochemistry of smooth muscle contraction), Grover C. Pitts (see above), and Rafael Rubio (cardiovascular physiology); Associate Professors Alex J. Baertschi (neuroendocrinology), Michael J. Cronin (neuroendocrinology), and Roger S. Fager (biochemistry of vision); and Assistant Professors Gary K. Owens (cell physiology of vascular smooth muscle) and Jeremy B. Tuttle (physiology of neurons and trophic factors). Former members of the full-time faculty

who have gone elsewhere include Louis A. Benevento, David H. Cohen, Mary D. Coyne, Joseph P. Gilmore, Thomas W. Lamb, Allan M. Lefer, Richard Odessey, S. Murray Sherman, Nick Sperelakis, David G. Ward, and Daniel E. Weiner. Five have taken chairmanships of physiology at other universities. We have been particularly fortunate in having joint appointees with their primary appointments in other departments who nevertheless contribute (or have contributed) significantly to our teaching and/or research programs. These include Ernst O. Attinger, Francoise M. L. Attinger, Luiz Belardinelli, Stuart S. Howards, Julian I. Kitay, Robert M. Mentzer, Jr., L. Clair Parsons, Edwin W. Rubel, Oswald Steward, and H. Richard Winn. Beyond the continued teaching of medical students, our teaching of graduate students has expanded equally. The department has awarded 44 Ph.D. degrees during Berne's tenure. Presently there are 18 graduate students, 1 Research Associate Professor, 2 Research Assistant Professors, 1 Research Instructor, 1 Research Associate, 1 Research Assistant, and 15 Postdoctoral Fellows in residence.

The departmental faculty has originated and/or participated in the following interdepartmental programs sponsoring research and/or offering degrees: the Vascular Smooth Muscle Program Project (3 departments), the Biophysics Program (12+ departments), and the Cell and Molecular Biology Program (7 departments).

Faculty research is prospering. All faculty research is well funded, and all eligible faculty hold, or have held, Research Career Development Awards of the National Institutes of Health or Established Investigatorships of the American Heart Association. The members of the current Physiology Department faculty serve, or have served, as editors and on editorial boards of prestigious journals, on important national committees, and as officers of various societies. All are participants in national and international scientific meetings.

Summary

In retrospect the progress of physiology as a discipline at the University of Virginia was slow but steady, with some static periods but hardly a discernible retrogression. Prior to the university's beginning, its founder Jefferson specified that physiology was to be taught. The distinguished and energetic first professor of physiology, Dunglison, emphasized the subject and taught it with enthusiasm, giving it local status which it could never have acquired under a lesser man. After the dynamic Dunglison years, the Board of Visitors and the faculty could never have countenanced any deemphasis of the subject. During the Civil War and the difficult Reconstruction Period, Cabell with his long tenure provided continuity and protected the subject from mortal blows. During the Pre-Modern Period Hough provided the trappings of a modern department: up-to-date laboratories, advanced courses, a journal club, and a theretofore absent emphasis on research in physiology for its own sake. Britton expanded the permanent faculty to three, expanded faculty research, and created a small but real graduate program with graduate students dedicated to physiology and receiving degrees in it; and Anslow modernized our renal physiology, which had been persistently antebellum in its quality. Crispell had the foresight and found the material support to initiate the Modern Period, and Berne provided the impetus to create the present department, which a recent Assessment of Research Doctorate Programs ranked 12th among 90 in the nation. Jefferson might agree that we have bettered his goal of making the University of Virginia the "capstone of education" in the Commonwealth.

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Funds Suspended After Animal Rights Groups Claim Abuse of Animals

Two research institutions have had their federal funds suspended after animal rights organizations claimed the facilities abused their laboratory animals.

Both institutions – the University of Pennsylvania and the City of Hope National Medical Center – were raided and vandalized last year by the underground Animal Liberation Front (ALF) and have been the targets of complaints to the US Department of Health and Human Services (DHHS) by People for the Ethical Treatment of Animals (PETA) and the Fund For Animals.

University of Pennsylvania . . .

The animal rights activist who led a four-day sit-in at the National Institutes of Health (NIH) has vowed to resume the sit-in should federal funding be restored to the Head Injury Clinical Research Center at the University of Pennsylvania.

Alex Pacheco, in a statement in front of the NIH headquarters after DHHS announced the suspension of funds to the University for its head injury studies, told his supporters: "I have received assurances from (both) Health and Human Services and NIH" that the research would not be resumed "and I promised to (James) Wyngaarden that if the experiments continue, he'll not only see 100 of us, he'll see hundreds of us."

Wyngaarden is the director of NIH, and Pacheco is the founder and chairman of PETA.

The sit-in by an estimated 100 animal rights activists climaxed a 13-month effort by PETA to end the federal support for the research at the University. The campaign was started after ALF broke into the University facility in May 1984, trashing the laboratory and stealing more than 60 hours of videotapes of the research conducted on baboons. The tapes were distilled into a 24-minute segment to show the primates struggling during a variety of experiments.

The decision to suspend the grant funds was made by DHHS Secretary Margaret Heckler. A final determination will be made after the University has had an opportunity to respond to questions about the head injury experiments.

The questions raised by NIH investigators indicate that the University failed, by and large, in its compliance with Public Health Service (PHS) policies for the care and use of laboratory animals.

Specific areas of concern cited in the NIH report involve supervision and training of laboratory personnel, management of anesthesia and analgesia for research animals, adequacy of techniques used to achieve a sterile environment, the extent of veterinary participation in certain aspects of the experiments, and the occupational health program in the head injury laboratory.

City of Hope . . .

All research funds were ordered suspended after NIH withdrew the City of Hope's certificate of assurance that the facility is in compliance with the "PHS Policy on Humane Care and Use of Laboratory Animals."

The Duarte, CA, institution was vandalized in December 1984 by ALF. The raid, which included the theft of 106 laboratory animals valued at $450,000, interrupted $500,000 worth of cancer, herpes, and emphysema research.

At the direction of NIH's Office of Protection from Research Risks, the City of Hope established a six-member committee with three members not affiliated with the institution. The committee reviewed the claims of the animal rights groups and reported several areas of noncompliance including administrative oversight, veterinary care, and the animals' physical environment.

NIH investigators have also visited the facility and are coordinating their efforts with the US Department of Agriculture, which also has been investigating the institution for possible violations of the Animal Welfare Act.

Like the University of Pennsylvania, the complaints found are largely in the management areas of research. Tom Galinski, administrator for the institution, said the problems indicated are correctable and will be corrected as soon as all of the findings of the investigations are complete.

Meanwhile, the one person who was arrested by police in northern California for possessing some of the cats stolen in the ALF raid at the City of Hope is still awaiting trial.

Revised NIH Guide Is Now Available

The newly revised edition of the "NIH Guide for the Care and Use of Laboratory Animals" is now available from two sources.

Single copies of the Guide may be obtained by writing the Office of Science and Health Reports, Division of Research Resources, Building 31, Room 5B-10, NIH, 9000 Rockville Pike, Bethesda, MD 20205. Bulk copies may be purchased by writing Superintendent of Documents, US Government Printing Office, Washington, DC 20402 or by calling (202) 783-3238. The publication number is 017-040-00498-2.

The Guide was revised by a special committee of the Institute of Laboratory Animal Resources of the National Academy of Sciences under contract from DHHS. The last previous revision of the Guide was in 1978.

The new Guide has an expanded bibliography and includes the addition of recommendations for new methods of cage ventilation and other housing requirements as well as some revisions in cage sizes.

Congressional Fundings

In one of its last acts before the summer recess the Congress approved a supplemental appropriations bill for fiscal year 1985, which included authorizations for the funding of 6,200 competing grants and 533 center grants by NIH and 550 center grants by the Alcohol, Drug Abuse, and Mental Health Administration. The Congressional action also permits NIH in fiscal year 1986 to carry forward as much as $20 million, providing all of the competing and center grants have been funded.

Both the House and Senate health-related appropriations committees plan to mark up fiscal year 1986 appropriations before the first session ends. Whether the number of grants remains unchanged or possibly lowered in 1986 will probably not be determined until some time in the second session.

The concurrent budget resolution for fiscal year 1986, passed by the Congress in August, calls for reductions in the spending ceilings for health and education programs, but ceilings on spending are determined by the appropriations committees.

If You Don't Succeed, Try, Try . . .

Both houses of Congress have again passed an NIH reauthorization bill, much like the one approved by the last Congress and vetoed by the President. The basic differences to be ironed out in the two bills by a conference committee is the length of time for the reauthorizations (Senate three years; House one year) and the establishment of an Institute for Nursing (House yes; Senate no).

Both bills included provisions for laboratory animals mandating institutional animal care committees, programs to develop alternative methods, and the promulgation of additional guidelines by the Secretary of DHHS.

William M. Samuels, CAE

APS Expresses Concern; DHHS Gives a Reply

In a letter to Health and Human Services Secretary Margaret Heckler, the American Physiological Society voiced its concerns regarding the events and the action that lead to the suspension of federal grant funds for the University of Pennsylvania's Head Injury Clinical Research Center. The Society's letter to the Secretary and the reply by the Acting Assistant Secretary for Health are reproduced below.

Honorable Margaret Heckler
Secretary
Department of Health & Human Services
Washington, D.C. 20201

Dear Secretary Heckler:

On behalf of the American Physiological Society, I am writing to express our concern that your action in acceding to the demands of demonstrators by suspending federal funds for trauma research at the University of Pennsylvania will only encourage militant advocates for animal rights to disrupt research programs. In recent years, the number of demonstrations and break-ins at research facilities by activists has increased as has the destruction to laboratory equipment and the theft of laboratory animals. By short-circuiting the normal processes for reviewing the situation at the University of Pennsylvania, you have rewarded these demonstrators for their sit-in at the National Institutes of Health and have encouraged them to escalate their activities, thus increasing the vulnerability of NIH and other institutions for further harassments.

Inasmuch as the Society has not had the opportunity to review the reports on which you based your judgments, your decisions are not being questioned on scientific grounds. Our concern, however, is that the Department of Health and Human Services, which has contributed so much to biomedical research, is now encouraging animal rights advocates to accelerate their efforts and supporting their appeal to the public by acceding to the demands. The timing and the circumstances of your action leads the scientific and academic communities to believe that you capitulated to the advocacy group and, thus, legitimized their activities. It is this action that raises the major concern now shared by most of the scientific community engaged in biomedical research.

Martin Frank
Executive Vice-President

Martin Frank, Ph.D.
Executive Vice-President
The American Physiological Society
Bethesda, MD 20814

Dear Dr. Frank:

This is in response to your letter of July 23 to Secretary Heckler regarding the suspension of the National Institutes of Health (NIH) funding for research with nonhuman primates at the Head Injury Clinical Research Center, University of Pennsylvania. We appreciate being apprised of your concerns and thank you for your candor.

There is no disputing your point that some people will misinterpret the suspension as a yielding to public pressure and a reward for unlawful advocacy. We were painfully aware that the NIH investigation had to rely heavily on copies of videotapes stolen from the University and we remain dismayed that law enforcement authorities have made no apparent progress in bringing the perpetrators to justice. Moreover, we recognize that the sit-in appears to have forced an administrative action the Department of Health and Human Services (HHS) was reluctant to take. As you know, the NIH was posed at the time of the sit-in to effect the suspension and was awaiting only the completion of the preliminary report so that the documentary basis of its action would be at hand and in a form consistent with due process. I assure you that before taking action, careful attention was given to all predictable misleading appearances.

On the other hand, I feel certain you will agree that a public agency must be prepared to discharge its responsibilities in accord with pertinent facts and applicable procedures and must not refrain from clearly indicated actions simply because some observers will misinterpret them. In the case of the head injury experiments with baboons, the NIH amassed disturbing evidence that the practices for the care and use of these laboratory animals during recent years were materially out of compliance with the University's written assurances. We view this breach of traditional trust relationship as a serious matter. The University's failure not only will make it more difficult for biomedical scientists to justify animal experimentation in the critically important area of brain injury but also may erode public confidence in the entire assurance system. Inaction (or delayed actions) by the HHS or the NIH under such circumstances would have been an abdication of our responsibility.

We remain convinced that the vast majority of biomedical scientists and their institutional officials are committed to proper care and use of laboratory animals and thus deserve the trust of the NIH. However, material failures of awardees to meet animal welfare requirements must produce firm and unequivocal responses on our part if the assurance system is to be sustained and be credible. We will continue to foster animal experimentation whenever such research gives promise of improving human health and is conducted in accord with our animal welfare requirements. At the same time, we will not hesitate to speak out against lawless practices by opponents of animal experimentation and will do everything we can to help law enforcement authorities combat such activities. We will work even harder to ensure that awardee institutions mean what their assurances say with respect to animal welfare.

I hope these comments are helpful.

James O. Mason, M.D., Dr.P.H.
Acting Assistant Secretary for Health

Committee Report

Animal Care and Experimentation

A meeting of the Animal Care and Experimentation Committee was held April 24, 1985 with Drs. Pullman, Krasney, Ramazzotto, and Fox (members) and Mr. Samuels (ex officio). Dr. Estrin, an anesthesiologist from the University of Minnesota and Sharon Martin attended as guests.

The major problem discussed and purpose of the meeting was, What to do about proposed changes in the APS Guiding Principles in the Care and Use of Animals.

This problem was raised by letters from Drs. Capranica, Fay, and Feng, who perform electrophysiological studies on hearing in frogs. All surgical procedures are performed under general anesthesia, and the animal is allowed to recover, local anesthetics also being used to prevent pain. Several days later, a microelectrode is inserted through the surgical opening while the animal is under a paralytic agent, and single unit recordings are made. No recordings are able to be obtained under any of the general anesthetics currently available. A similar problem exists in eye research (letter of Dr. Geller, NIH). An additional aspect of this problem was raised by Dr. Abraham Rudolph, who studies sheep fetuses, the mother being under spinal anesthesia, local anesthetics only being used on the fetuses with muscle relaxants being added recently to the fetal studies to permit manipulation of the fetus to expose specified fetal parts.

The committee agreed that the Society would be best served if we retained the guidelines as they stand, without revision, in order to permit the greatest flexibility to the investigator. In the last analysis, the good judgment of the scientist would prevail, with the local (institutional) animal care committee providing guidance and supervision.

It was agreed, as suggested by Dr. Ramazzotto, that Council consider an educational program to inform members about the advantages of AALAC accreditation, the more institutions having such accreditation the fewer difficulties our membership would encounter. It was also suggested that the Council encourage appearances by the members before the public, e.g., on local TV or radio, so that the public will be presented with both sides of this important issue of the use of animals in research. Mr. Samuels of the APS office should be contacted as a resource person prior to such appearances so that the speakers will receive appropriate data on this subject, as well as information about unfair practices which have sometimes been used under these circumstances by the opposition.

Dr. Krasney mentioned that, at SUNY Buffalo, he has instituted a panel discussion at the beginning of the freshman year regarding the use of animals in the teaching laboratory. A philosophy professor, a clinician, and a basic scientist are included on the panel, and this has obviated difficulties which students sometimes have with teaching laboratories. The committee agreed that the Council should encourage this approach.

The letter from Dr. Rackow, Professor Emeritus, Columbia University, College of Physicians and Surgeons, calling for stricter regulation was taken under advisement.

The second problem was a letter from Dr. Kohn of the American Veterinary Association requesting guidance on the use of physical methods of euthanasia, which appeared somewhat confusing in that stunning was suggested as a form of euthanasia, which it is not. It was agreed that physical methods of euthanasia such as decapitation, cervical dislocation, etc., require special training, but it was felt best to leave the responsibility for this in the hands of the local investigator and local animal care committee.

With regard to the letter by Dr. Robertshaw of the College of Veterinary Medicine, Colorado State University, concerning what he and Dr. Bernard Rollin regard as a problem, namely, "the lack of standards of care and use for domestic farm animals employed in biomedical research," stating that these are "legally 'unprotected' animals," the committee felt that it has never been the Society's policy to have a hierarchy of animals as far as the humane treatment of animals is concerned. It has always been the Society's policy to treat all animals used in research humanely, regardless of whether they are so-called farm animals or not. Thus Dr. Robertshaw's suggestion that there exists in our membership "the notion of 'first and second class animals' " is a straw man which requires no action by the Society. To use Dr. Robertshaw's words, "the extending of legal protection and guidelines to all animals" is, in the Committee's opinion, unnecessary in that this is already the case.

I. J. Fox, Chairman

Future Meetings

1986	
FASEB Annual Meeting	April 13-18, St. Louis
IUPS Congress	July 12-20, Vancouver, Canada
APS Fall Meeting	October 5-10, New Orleans
*FASEB Annual Meeting	March 29-April 3, Washington, DC
APS Fall Meeting	October 11-16, San Diego
1988	
FASEB Annual Meeting	May 1-6, Las Vegas
Joint APS/ASPET Fall Meeting	October 9-14, Montreal
*APS Centennial Celebration	

Procter & Gamble Fellowship

Darlene Racker, an APS Porter Development Fellow, is the recipient of the 1985-86 Procter & Gamble Fellowship in Physiology. As a Procter & Gamble Fellow, she will receive a cash award of $9,500 to assist her in the completion of a Ph.D. degree.

Honors & Awards

Symposium on Nidation Held in Honor of M. C. Shelesnyak

A Symposium on Nidation was held at McGill University, Montreal, on July 22, 1985, in honor of Professor M. C. Shelesnyak. Dr. Shelesnyak, elected to membership of APS in 1948, is a pioneer in the study of nidation, the embedding of the embryo in the uterine mucosa. He is the originator of the histamine theory of nidation which did much to stimulate further research in the area. Before his retirement, Dr. Shelesnyak was associated with the Smithsonian Institution as Director of the Interdisciplinary Communications Program, the Weizmann Institute of Science, Rehovoth, Israel, where he was Professor and Head of the Department of Biodynamics, and the Office of Naval Research.

The symposium began with a historical review of nidation research by Dr. Shelesnyak and Dr. G. J. Marcus. Papers dealt with the endocrinological, physiological, biochemical, and immunological aspects of blastocyst implantation and decidualization; embryonic signals for induction of implantation; the sensitivity of the uterus for implantation; and an in vitro model for implantation research. Dr. Koji Yoshinaga is editing the papers for publication by the New York Academy of Sciences.

Dr. Shelesnyak, known to friends as "Shelly," has been a familiar figure at APS Headquarters for the past several years. He served as APS Centennial Task Force Director from 1978 to 1985, stepping down upon his recent move to California, and played a major role in getting the Centennial program off to a good start.

Knut Schmidt-Nielsen Honored

Knut Schmidt-Nielsen, Professor of Physiology, Duke University, was recently awarded the degree of Honorary Doctor of Medicine by the University of Lund, Sweden. This summer, he also received the high honor of an invitation to become a foreign member of The Royal Society. Dr. Schmidt-Nielsen, a member of APS since 1949, is President of the International Union of Physiological Sciences. He is the editor of *News in Physiological Sciences*, a joint publication of APS and IUPS, which will make its first appearance in February 1986.

Celebration of E. F. Adolph's 90th Birthday

A scientific symposium was held on September 28 at the University of Rochester in honor of the 90th birthday of Edward F. Adolph. Dr. Adolph, Professor Emeritus of Physiology at the University of Rochester, has been associated with the School of Medicine and Dentistry since its opening. A special announcement was made at the birthday celebration that one of the large auditoriums in the Medical Center was to be named in his honor. Dr. Adolph has been a member of APS since 1921, making him one of our two earliest elected living members. He served as President of APS in 1953. In 1984, he was the recipient of the Ray G. Daggs Award for his many contributions to physiology and to the Society (*Physiologist*, 27(3): 150-151, June 1984).

News From Senior Physiologists

Frank H. Johnson to Arthur Otis:

Nothing very exciting to report. Various circumstances make it no longer possible for me to work in a laboratory, but I enjoy giving occasional informal talks on bioluminescence with demonstrations of chemiluminescences such as the "luminol reaction," using blood as the catalyst, with Clairoxide hair bleacher as a source of peroxide, and solid Drano to make the solution alkaline. In the absence of the usual laboratory facilities I have to resort to what happens to be available from general sources. To an uninitiated audience the results seem spectacular, enhanced by adding ice cubes to the brightly glowing solution to emphasize its nature of "cold light."

Most of the writing I have done over the years has been purely technical. Following mandatory retirement, however, I have aspired to come up with several manuscripts in a more popular vein. Perhaps the most notable has been a book entitled *A Letter to Three Daughters*, "published" in a very limited edition of six hardbound copies, containing over 300 xeroxed pages each, of which I am the author, editor, publisher, and perpetrator. The book is both a biography of the three children, from birth to adults, illustrated by photographs which have survived the ravages of time and of just plain getting lost. It is also autobiographical, including time when they could not have known me before they were born or were to young to remember.

I have managed to maintain my alter ego in the field of Art, painting in oil or water color, and sketching from life in charcoal. My wife is impressed with what she calls my "Rogues Gallery" of famous scientists portrayed in charcoal. I was invited just last year to do a water color for a special exhibit by New Jersey artists in celebration of the Sesqui-Centennial of the opening of the Delaware-Raritan canal, which for a time was an important transportational segment between Philadelphia and New York.

590 Lake Dr.
Princeton, NJ 08540

Hermann Rahn to Arthur:

Let me tell you how much I enjoy reading the Senior Physiologists column in every issue of *The Physiologist.* At the end of the summer I will be exploring the diffusion-perfusion relationships in the incubating hen's egg. I am still working on various other aspects of bird eggs in general and hope to write a book on this topic for the zoologists. I just received my first copy of a new book which I edited on "Acid-Base Regulation and Body Temperature." This is a small volume with contributions by three basic scientists and three clinicians, hoping to give some new ideas on how to treat the 150,000 patients that undergo cardiac bypass operations during hypothermia each year. There were no field expeditions this year—I miss them.

State University of New York at Buffalo
Buffalo, NY 14214

Florent E. Frank to Roy Greep:

Thanks very much for your greetings and well wishes from the American Physiological Society on my ninetieth birthday. It added something special hearing from my scientific associates. We had several family celebrations and even had a good fishing trip. My grandchildren came from Dallas, Madison, and Kansas City to help celebrate. It was a very happy occasion.

St. Louis, MO

Donald Whedon to Roy:

Following my retirement in September 1982 from NIH, the last 19 years as Director of NIADDK, I managed the conferences program of the Kroc Foundation in Santa Ynez, CA, until the Foundation became scheduled for dissolution. Meanwhile, by 1983 the research projects program of the Shriners Hospitals system had grown to sufficient size (70 projects and $8.5 million) that a professional manager was needed. Consequently in June 1984 I moved from California to Shrine Headquarters in Tampa; as Consultant for Medical Research Programs, I work "waltz time" (3/4 time to nonmusicians), facilitating studies on burns and various bone diseases for a splendid organization. The other 1/4 time I spend variously reviewing an occasional paper, talking a couple of times a year on some aspect of osteoporosis at a symposium or conference (sometimes published), serving on the US Committee of the US-Japan Cooperative Medical Science Program, and meeting with various NASA research planning groups, notably the NAS-Space Science Board-sponsored "Major Directions for Space Science" (Life Sciences Task Group thereof). My golf game is still suffering from neglect, but not my suitcase.

Shriners Hospitals
P.O. Box 25356
Tampa, FL 33622

Herbert Pollack to Roy:

Thank you very much for your note recognizing my eightieth birthday. I continue an active life. March I went to Dallas for the wedding of my nephew's daughter; April to London (England) for a chess match; May to San Diego, California, as an invited speaker at the annual meeting of the Electromagnetic Energy Policy Alliance on medicolegal aspects; June to Newark, New Jersey, as an expert consultant at a hearing for a new Microwave Relay Station. I continue my appointment as Consultant to the US Department of State. I continue to write. It is only by the use of my IBM PC with a modem and word processing software that I am able to carry out a heavy schedule. I do my library search from my desk tapping into the data banks of the National Medical Library and any other that I may need for reference through Dialog, saving endless hours of travel in traffic. This letter is being written on my word processor, enabling an adequate typist to look professional.

This winter Mrs. Pollack and I are planning a cruise for two months, from Fort Lauderdale through the Panama Canal across the Pacific to New Zealand and Australia, up through the Islands to Hong Kong, where we leave the ship and fly up to Bejing for several days to visit a long-time friend who is stationed there. Back to Hong Kong and fly back to the States from there.

100 Worth Ave.
Palm Beach, FL 33480

Paul Kezdi to Bob Alexander:

I retired July 1984 after eight years of service as Associate Dean for Research Affairs of the Wright State University School of Medicine of Dayton, Ohio. This gave me the opportunity to again dedicate myself to my first love, cardiovascular research, continuing as Director of the Cox Heart Institute. Simultaneously, I agreed to serve on a part-time basis as Medical Director of Jerrold R. Petrofsky's spinal cord injury research at the National Center for Rehabilitation Engineering of Wright State University. I am continuing by baroreceptor research with my co-workers and have concentrated predominantly on the cardiopulmonary reflexes. We have correlated physiological responses conducted by vagal afferents from the atria and ventricles by tagging the receptors and histologically identifying their central terminations. We are analyzing our data for publication. We have done preliminary studies on the role of the cardiopulmonary reflexes in the regulation of the circulation in spinal cord-injured humans with cervical and high dorsal cord damage. We are using lower body negative pressure and forearm plethysmography to study the reflex effect on forearm blood flow, renin aldosterone, and vasopressin release in spinal cord injury and plan similar studies in hypertension to elucidate the role of cardiopulmonary reflexes in the mechanism of hypertension. I became interested a few years ago in cell membrane mechanisms, particularly the sodium pump, in hypertension and presented at a satellite symposium of the International Society of Hypertension meeting in 1984, "Mechanism of diuretic induced hypotassemia, its effect on total body potassium, and the Na^+-K^+-ATPase in human hypertension." All this is a lot of work, which I enjoy even more after relinquishing much of my administrative responsibilities. I have gathered some material for writing some time in the future, if time allows, my memoirs. I had the good fortune to personally know some of the great men of science such as Albert Szentgyorgyi, Corneill Heymans, Carl Wiggers, Hans Selye, Harry Goldblatt, just to mention a few.

Cox Heart Institute
3525 Southern Blvd.
Dayton, OH 45429

Oxygen Transport: A Simple Model for Study and Examination

KERMIT A. GAAR, JR.
Department of Physiology and Biophysics
Louisiana State University Medical Center
School of Medicine in Shreveport
Shreveport, Louisiana 71130

Under normal conditions, the O_2 capacity of blood is almost perfectly matched to the atmospheric air, since 100 ml of each contains about 21% O_2. In blood, this is made possible by the presence of highly soluble hemoglobin, which increases the amount of O_2 the blood can carry by 30-fold over that which is normally dissolved in water. In doing so, the hemoglobin is able to "correct" for the dilution of the atmospheric air in the alveoli by water vapor and CO_2. In conjunction with this three factors mainly determine the amount of O_2 that can be carried from the lungs to the tissues each minute: *1*) $P_{A_{O_2}}$—the pressure of O_2 in the alveoli sets the upper limit for the P_{O_2} of oxygenated blood leaving the lungs; *2*) hemoglobin concentration—this determines the amount of "bound" O_2 that the blood can carry at any given P_{O_2}; and *3*) cardiac output—this determines the rate of O_2 delivery to the tissues.

If any one of the above factors were to become severely depressed or if all were affected to a moderate degree at the same time, then sufficient O_2 might not be available to the tissues to meet their metabolic needs. A computer model can facilitate the quantitative study of these basic relationships.

Figure 1 shows the block diagram of a simple O_2 transport model. Block 1 of Figure 1 shows a relationship between the $P_{A_{O_2}}$ and the O_2 concentration of arterial blood (Ca_{O_2}). Ordinarily, these two variables are affected by complex factors governing diffusion of O_2 at the pulmonary membrane and its uptake by erythrocytes. There is also the effect of some shunting due to the so-called venous admixture, as well as pH, P_{CO_2}, etc. that have important effects at the capillary level, but these have been purposely omitted because they would only add to the model's complexity without significantly enhancing its heuristic value. Instead, block 1 simply shows that the pressure of O_2 in the blood equilibrates with the $P_{A_{O_2}}$ as the blood becomes saturated with O_2 in its passage through the lungs.

The other factor that affects the O_2 content of the blood at any given P_{O_2} is the *slope* of the oxyhemoglobin dissociation curve. This is set by the "capacity" of blood to load on O_2 as the P_{O_2} rises which depends on the concentration of hemoglobin ([Hb]) in the blood. Three different [Hb] are provided in the model. In addition to a normal value of 15 g/100 ml of blood, there are 10 and 5 g/100 ml levels.

In block 2 of Figure 1 the Ca_{O_2} is multiplied by the cardiac output to give the rate of O_2 delivery to the tissues ($\dot{V}a_{O_2}$). In block 3 the rate of O_2 usage by the tissues ($\dot{V}c_{O_2}$) and the rate at which unused O_2 is returned to the lungs ($\dot{V}v_{O_2}$) are subtracted from $\dot{V}a_{O_2}$. The result of this is accumulated at block 4 to determine the total O_2 content of the peripheral venous blood ($\dot{V}v_{O_2}$). In block 5 the O_2 content of the blood is divided by the venous blood volume (Qv) to give the O_2 concentration (Cv_{O_2}). The Ca_{O_2} then returns to block 6, where it is multiplied by the cardiac output to give the rate at which O_2 is transported back to the lungs. Cv_{O_2} also enters block 7, which is similar to block 1, except that the axes are transposed; this allows conversion of Cv_{O_2} to O_2 pressure (Pv_{O_2}).

The O_2 transport model program was written in Applesoft BASIC for implementation on an Apple microcomputer (Apple Computer, Cupertino, CA), but the program can be modified to run on other computers that support the BASIC programming language.

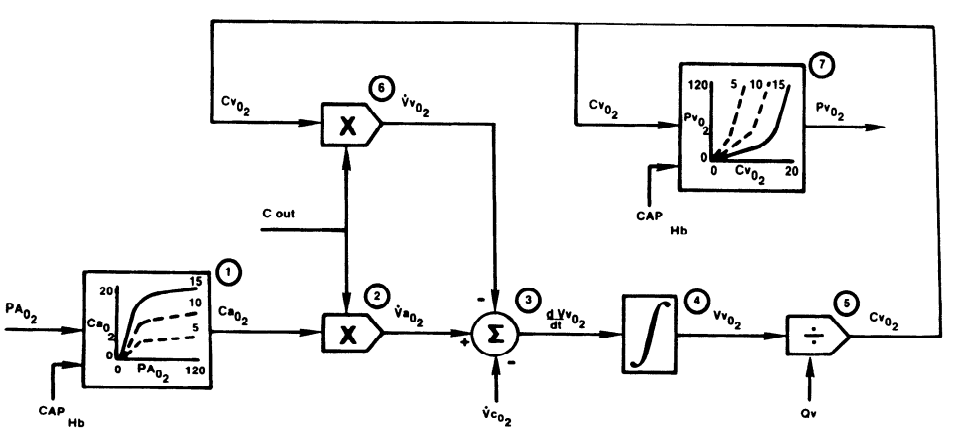

Figure 1
Block diagram for simple O_2 transport model. A brief description of the model is given in text, including an explanation of symbols.

An important feature of the model is the way in which the information is output to the TV screen. First, there is a continuous plotting of the alveolar and venous blood O_2 pressures in a high-resolution (HIres) graph display. Next, the current values of five important variables are printed underneath the HIres picture. The variables are *1*) the amount of time lapse from the beginning of the simulation; *2*) the arterial blood O_2 concentration; *3*) the alveolar O_2 pressure; *4*) the venous blood O_2 concentration; and *5*) the venous blood O_2 pressure.

```
1-RESUME SIMULATION
 2-CHANGE PARAMETERS
  3-PRINT CURRENT DATA
   4-START NEW SIMULATION
    5-QUIT THIS SIMULATION

   SELECTION -> 2

CHANGE ALVEOLAR PO2 (Y OR N) :N

CHANGE CARDIAC OUTPUT? (Y OR N) :N

CHANGE OXYGEN UTILIZATION? (Y OR N) :Y

OXYGEN USE NOW (250) ML/MIN
NEW O2 UTILIZATION (ML/MIN)? :750

ARE THESE VALUES CORRECT (Y OR N)? :Y
```

Figure 2

This shows 5-selection menu that appears on TV screen anytime a keyboard key is pressed while program is running. Also shown is some of the dialog following selection of option 2. In this example the operator has increased O_2 usage to 3 times the normal rate.

```
C.OUT= 50 X100 ML/MIN  HGB= 15 G/100ML
O2 USE= 250 ML/MIN  UTIL.COEF= 25%
TIME     A%O2     APO2      V%O2     VPO2
 50     19.63    100      14.63    43.5


C.OUT= 50 X100 ML/MIN  HGB= 15 G/100ML
O2 USE= 250 ML/MIN  UTIL.COEF= 29%
TIME     A%O2     APO2      V%O2     VPO2
 250     16.81    50       11.82    35.1
```

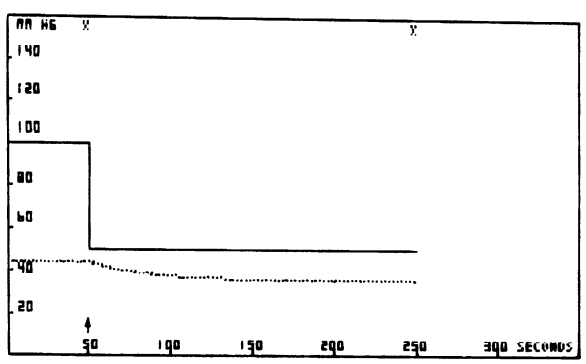

Figure 3

Decreased $P_{A_{O_2}}$ (see text for explanation). At the 50-s mark (arrow) $P_{A_{O_2}}$ was reduced to 50 Torr (mmHg). Picture shown here (and Figures 4 and 5) is a facsimile of HIres picture on TV screen reproduced by dot-matrix type of printer. Listings of variables shown above HIres picture represent values current at the times indicated, corresponding to × symbols that appear at various locations along top border of picture that were placed there automatically during simulation whenever a listing was ordered. Abbreviations are as follows: C.OUT, cardiac output; HGB, hemoglobin concentration; O2 USE, rate of O_2 useage; UTIL.COEF, O_2 utilization coefficient; A%O2, percent O_2 in arterial blood, ml O_2/100 ml blood; APO2, alveolar O_2 tension, Torr; V%O2, percent O_2 in venous blood, ml O_2/100 ml blood; VPO2, venous blood O_2 tension, Torr. *Solid tracing* represents alveolar $P_{A_{O_2}}$; *Dashed tracing* represents $P_{v_{O_2}}$.

Simply pressing any key on the computer keyboard will halt the simulation and bring up a menu page on the TV screen in place of the graph. One of the menu selections (selection 3 in Figure 2) causes the current values of the above five variables to be printed on a printer connected to the computer. In addition to these, other data are sent to the printer consisting of the current values of *a*) cardiac output; *b*) the [Hb]; *c*) the rate of O_2 usage; and *d*) the O_2 "utilization coefficient," which is the fractional amount of available O_2 that is removed from the blood during its passage through the tissues. Immediately after these data are printed, the graph returns to the screen with an × marking along the top axis corresponding to the place in time that the event occurred. This is helpful in correlating the printed data with the graph, especially when there are repeated simulation runs on a single graph which is an option made available through menu selection 4. Whenever menu selection 4 is chosen the operator is given the option of overlaying a new simulation on the current graph or starting over with a completely new graph. If an overlay is selected, then the current graph is left on the screen while the simulation starts over from the beginning of the screen. This is very useful for demonstrating the different effects that might be obtained when different parameters are changed, as will be described next.

Except for the [Hb], which is selected at the very beginning, the model's parameters can be changed at any time during a simulation. Pressing any key on the computer keyboard halts the simulation and calls up the numbered menu of selections on the TV screen as shown in Figure 2. In this example the operator has opted for selection 2, "change parameters." After replying with a (Y)es, each parameter is presented in turn and the operator has the option to change or not to change it to some other value. To help the operator, the current value of each parameter to be changed is printed also.

An example of changing parameters during a simulation is shown in Figure 3. In this example the effect of reduced $P_{A_{O_2}}$ on O_2 transport is shown. This is similar to the effect that would occur when pulmonary ventilation is decreased to one-half normal or when one ascends to a high altitude (15,000 ft) while breathing air. Despite the fact that $P_{A_{O_2}}$ has been cut in half, the $P_{v_{O_2}}$ has fallen only slightly, from 43 down to 35 Torr. Also, the percentage of O_2 removed from the blood, indicated by the utilization coefficient mentioned previously, has increased from the normal value of 25% up to 29%. Such a small change would not be expected to cause any difficulty. The reason, of course, is explained by the shape of the oxyhemoglobin dissociation curve that can be found in human physiology textbooks. This will show that the blood P_{O_2} can fall to 60 Torr while the blood is still 90% saturated with O_2. The student might want to investigate the effect of a much greater reduction in the $P_{A_{O_2}}$, such as might occur following a sudden loss in cabin pressure while flying in an airplane at 30,000 ft ($P_{A_{O_2}}$ = 21 Torr). On the other hand, a different type of experiment might involve elevating the $P_{A_{O_2}}$ to very high levels to examine the effects of O_2 carried by the blood in the dissolved state.

One of the most important functions of hemoglobin is to ensure that sufficient O_2 is delivered to the tissues even though the total amount of O_2 available is reduced. The hemoglobin does this while keeping the P_{O_2} from falling very much while O_2 is rapidly unloaded to the tis-

sues during times of increased need. This has been called the "O_2-buffering function of hemoglobin." Most textbooks attribute this to the steep slope of the hemoglobin-O_2 dissociation curve but say very little about how it is related to the concentration of hemoglobin in the blood. This is demonstrated in Figure 4. The three lower dashed tracings shown in Figure 4 represent the venous blood Pv_{O_2} values that would result from different blood hemoglobin concentrations. With normal [Hb], the Pv_{O_2} is about 43 Torr. When the [Hb] is reduced to two-thirds normal the Po_2 falls only 7 Torr (from 43 down to 36 Torr). Further reduction in the [Hb] to one-third normal causes the Po_2 to fall an additional 21 Torr (from 36 down to 15 Torr), which is a threefold greater change than before. In other words, the "O_2-buffering capacity" of hemoglobin changes when its concentration changes, just like that of an acid-base buffer that prevents wide changes in pH which, as it happens, also depends on the concentration of the buffer.

To appreciate the physiological significance of this, it is important to know that the Po_2 of the interstitial fluid bathing the cells can never be higher than the Po_2 of the venous blood returning to the lungs. Also, most cells are seldom more than a few microns distance from a capillary. For these reasons, the Po_2 of the venous blood leaving the tissues is often a good indicator of the average state of tissue oxygenation. This is because it is determined by a balance between *a*) the rate of O_2 delivery to the tissues by the blood and *b*) the rate at which the O_2 is used by the tissues. An example of this is illustrated in Figure 5, which shows the results of two successive simulations. First, in the tracing indicated by the letter A on the graph of Figure 5, the effect on Pv_{O_2} of a decrease in tissue metabolism is shown. Near the 50-s mark the simulation was stopped to change parameters using selection 2. In this example the rate of O_2 usage was decreased to one-third normal. This caused the Pv_{O_2} to climb to 54 Torr. Following this, the simulation was stopped to begin another simulation using selection 4. The graph overlaying option was chosen to retain the results of the previous simulation. Near the 50-s mark the simulation was stopped again to change parameters. In this second example, indicated by the letter B on the tracing, the rate of O_2 usage was increased to three times normal to simulate an increase in tissue metabolism. This time the Pv_{O_2} fell to 14 Torr. In summary, while tissue metabolism was able to change 600% overall, the total variation in Pv_{O_2} was <100%.

For further study, the student might want to repeat the last experiment, except this time, study the effect of changes in blood flow on Pv_{O_2} and then compare this with the metabolism experiment. This might then suggest other experiments involving combinations of the two. As a suggestion, the student could investigate the combined effects of a concurrent increase in both tissue metabolism and blood flow similar to what occurs during exercise. For example, during heavy exercise arterial Po_2 does not change significantly, whereas Pv_{O_2} might fall to 20 Torr. With this information, one question that could be answered is, "How much of an increase in metabolism, as indicated by the rate of oxygen usage,

```
C.OUT= 50 X100 ML/MIN  HGB= 15 G/100ML
O2 USE= 250 ML/MIN  UTIL.COEF= 25%
TIME     A%O2     APO2      V%O2     VPO2
 100     19.63    100     14.63    43.5

C.OUT= 50 X100 ML/MIN  HGB= 10 G/100ML
O2 USE= 250 ML/MIN  UTIL.COEF= 37%
TIME     A%O2     APO2      V%O2     VPO2
 150     13.18    100     8.18     36.3

C.OUT= 50 X100 ML/MIN  HGB= 5 G/100ML
O2 USE= 250 ML/MIN  UTIL.COEF= 74%
TIME     A%O2     APO2      V%O2     VPO2
 200     6.74     100     1.74     15.2
```

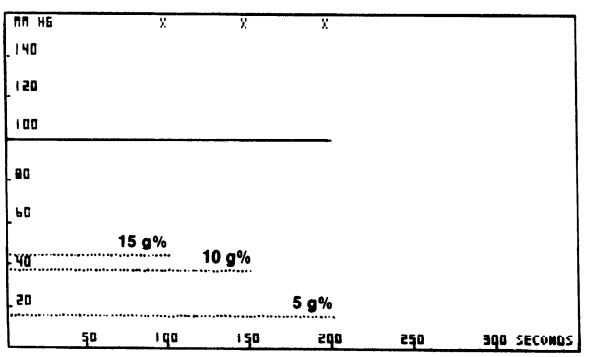

Figure 4

O_2-buffering function of hemoglobin (see text for explanation). This picture is a composite of 3 different simulations. *Solid tracing* represents Pa_{O_2}; *dashed tracings* represent effects of different hemoglobin concentrations on Pv_{O_2}. All tracings were able to be put on one picture by using an "overlaying" feature of the model program as explained in text.

```
C.OUT= 50 X100 ML/MIN  HGB= 15 G/100ML
O2 USE= 250 ML/MIN  UTIL.COEF= 25%
TIME     A%O2     APO2      V%O2     VPO2
 49      19.63    100     14.63    43.5

C.OUT= 50 X100 ML/MIN  HGB= 15 G/100ML
O2 USE= 83.32 ML/MIN  UTIL.COEF= 8%
TIME     A%O2     APO2      V%O2     VPO2
 249     19.63    100     17.95    53.7

C.OUT= 50 X100 ML/MIN  HGB= 15 G/100ML
O2 USE= 750 ML/MIN  UTIL.COEF= 76%
TIME     A%O2     APO2      V%O2     VPO2
 300     19.63    100     4.64     13.8
```

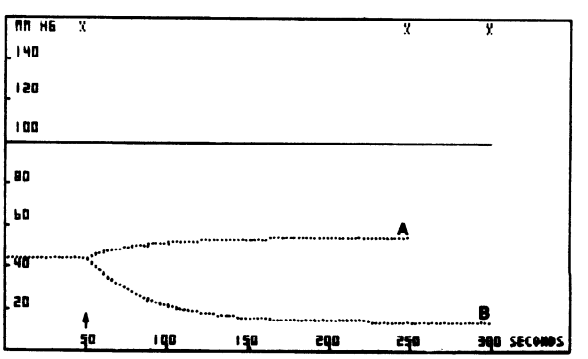

Figure 5

Tissue metabolism changes (see text for explanation). The solid tracing represents Pa_{O_2}. *Dashed tracings,* represent results of separate simulations: *A*) at the 50-s mark (arrow) during the first simulation, the rate of O_2 usage was decreased to one-third normal; *B*) a second simulation was run using the overlaying feature, but this time the rate of O_2 usage was increased to 3 times normal.

can be supported by an increase in cardiac output to the maximum permissible level?" To do this, one would first increase the cardiac output to five times normal and then make subsequent adjustments upward in the rate of O_2 usage until the Pv_{O_2} falls to about 20 Torr. The rate of O_2 usage at this level would be indicative of the maximal level of metabolism that could be achieved under these circumstances. The experiment might be repeated, but with a reduced [Hb] to simulate the effect of anemia.

In conjunction with the experiments suggested above the student should pay special attention to the transient nature of the changes in the variables. The graph overlaying feature of the model is particularly effective for this. For example, study the transient effects of several different hemoglobin concentrations or rates of O_2 utilization with the cardiac output level set to normal, and again, with the cardiac output set to some different level.

Some additional suggestions for study are part of the documentation that has been prepared for the model program. This documentation has a complete program listing, a listing and description of all the variables, constants, and other parameters in the program, and all the instructions needed to run the program. Apple DOS 3.3, Applesoft in ROM and a minimum of 48K RAM are required. To obtain a copy of the documentation and software, send a blank diskette to K. A. Gaar, Jr., Dept. of Physiology and Biophysics, L.S.U. Medical Center, P.O. Box 33932, Shreveport, LA 71130.

Book Reviews

Underwater Physiology VIII

A. J. Bachrach and M. M. Matzen (Editors)

Bethesda, MD: Undersea Med. Soc., 1984, 770 pp., illus., index, $60.00

This handsome well-edited volume is the current member of a series that began in 1955 with the small paper-covered proceedings of the first Underwater Physiology Symposium. The difference between I and VIII symbolizes the growth in stature of the field concerned. *Underwater Physiology* has come to include all aspects of physiology that involve ambient pressures above normal barometric levels, immersion, and other factors in diving, work in compressed air, and hyperbaric treatment of medical conditions. These interests also relate to a surprising number of other areas of medicine and physiology.

The "underwater" field is now represented by the Undersea Medical Society, which covers these interests with a respected research journal, a newsletter, an abstracting service reflected in two review journals and periodic bound volumes, annual scientific meetings, workshops on special topics, and well-produced hardcover books like the present volume.

The Society is one of the sponsors of the Underwater Physiology Symposia. These now are held at 3-year intervals, most often outside the U.S.A. They draw several hundred attendees, and the present volume lists over 150 contributors from almost all parts of the world. The Eighth Underwater Physiology Symposium was held in Canada in 1983, and the proceedings were published within the following year.

The volume is made up of the manuscripts of original reports and invited reviews on topics including oxygen toxicity, inert gas exchange and decompression, respiratory and circulatory effects, thermal factors, molecular and cellular effects, and neurologic and behavioral consequences of hyperbaric exposure. The reviews are valuable not only for those familiar with the area concerned but especially so for those with a beginning interest. Almost all of the individual papers represent previously unreported work with only enough reference to previous studies to provide needed background.

With both reviews and papers, *Underwater Physiology VIII* is a valuable text as well as a "progress report" for its field. As such, it can serve especially well as a resource for related research and clinical interests. The book is too costly to recommend for acquisition by many individuals, but it should be in most medical libraries, on many laboratory bookshelves, and also in some engineering libraries.

Having said this, the reviewer must express his opinion that the purposes of the Underwater Physiology Symposia and their costly proceedings now are, or readily could be in the future, served more promptly and economically by ongoing functions and publications of the Undersea Medical Society. Also, his respect for volumes of this quality is entirely offset by the shorter times and lower costs of proceedings reproduced directly from "camera-ready" manuscripts for which the authors must assume full responsibility.

Edward H. Lanphier
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A Guided Tour of the Living Cell

Christian de Duve

New York: Sci. Am. Books, 1984, 423 pp., illus., index, $55.95

The cell is the minimal organization of matter and energy that exhibits all of the activities characteristic of life. *A Guided Tour of the Living Cell* provides a unique perspective on this magnificent product of billions of years of evolution, with emphasis on the eukaryotic cell. By conceptually shrinking his readers 10^6-fold in linear dimension relative to the cell, the author, Dr. Christian de Duve, converts the readers into "cytonauts," explorers of a mysterious and beautiful cytological realm.

Dr. de Duve is, of course, eminently qualified to guide such a journey. Winner of the 1974 Nobel Prize in medicine, together with Albert Claude and George Palade, he is the discoverer of the "lysosome" and the "peroxisome" and is a founder of the field of modern cell biology. That he is also an articulate, witty, charming, and skillful expositor of his subject is made strikingly clear by this handsome two-volume set. An addition to the Scientific American Library Series, Dr. de Duve's *Tour* originated in a four-hour lecture presented to 550 selected high school students as the Alfred E. Mirsky Christmas Lecture of the Rockefeller University in 1976. Dr. de Duve is Andrew W. Mellon Professor at the Rockefeller University.

Part of the uniqueness of this book lies in its level of exposition. The book assumes no prior knowledge of cell biology and provides basic chemical background as needed in a series of interludes and appendices. It is therefore accessible to intelligent readers of all backgrounds. Nevertheless, the author never "writes down" to the reader, but rather he avoids oversimplification and superficiality. Most of the major topics of modern cell biology are touched on and usually explored with provocative insight and suggestive speculation. Indeed, the uniqueness of the approach makes the book of interest and value even to professionals who are thoroughly familiar with the subject matter, since it offers the delight of viewing the cell with a new perspective.

Dr. de Duve's wit and imagination are evident throughout this exploration of the eukaryotic cell. As the "cytonauts" approach the cell, for example, they encounter a tangle of extracellular protein and proteoglycan fibers which are compared, in words and pictures, to the vines and trunks of the Amazon rain forest. (We are treated to a vista of thick collagen trunks and a tangle of proteoglycan lianas.) Here and throughout the book the high level of Neil Hardy's artwork adds immeasurably to the clarity and appeal of the text. Characteristically, the encounter with extracellular protein leads the reader into a brief but satisfying introduction to protein structure.

Entry of the "cytonauts" into the cell itself is effected by endocytosis, beginning the first of three "itineraries," an exploration of the cell surface and of the "vacuome" (the system of vesicles, vacuoles, granules, Golgi apparatus, and endoplasmic reticulum that allows materials to enter, leave, or be transported within the cell while remaining separated from the cytosol by segregation within membranes). Membrane properties and membrane flow are considered in detail, and as one might expect from their discoverer, the function and role of lysosomes are explored in fascinating detail.

Using acid-triggered ejection "jackets" borrowed from viruses, the "cytonauts" plunge into the cytosol (ground cytoplasm) itself; this initiates the second "itinerary." The exploration of the cytosol and its embedded organelles provides an opportunity for an extensive introduction to cell metabolism, including fermentation, respiration, photosynthesis, group transfer and biosynthesis in general. The treatment of topics is clarified by the use of picturesque terms such as "oxphos units" and "Janus, the double-headed intermediate" (of group transfer in biosynthesis), yet oversimplification is avoided. The roles of peroxisomes and other microbodies are explained and the "cytonauts" are treated to a fascinating and up-to-date overview of "cytobones and cytomuscles." Surveys of membrane action, metabolic regulation, and the flow of biological information during protein synthesis by ribosomes complete the second journey.

The third "itinerary" takes the "cytonauts" into the cell nucleus. Here, the genes and chromosomes are explored in intriguing detail. Mitosis and meiosis are encountered in all their drama and intricacy and, with the author's characteristic imagination, the turmoil of cell division is used as an opportunity for egress of the "cytonauts" from the nucleus and then from the cell itself.

The book could more accurately be entitled *A Guided Tour of the Eukaryotic Cell.* This is not to say that prokaryotic cells are completely neglected. A series of comparisons and contrasts with bacteria scattered through the book gives the reader a responsible idea of prokaryotic structure and function. We have in recent years become more appreciative of the complexity of organization and evolutionary history of the prokaryotic cell. Surely someday the bacteria will also have their Homer, and I hope that he will do as spectacular a job as Dr. de Duve has done for the eukaryotic cell.

I have few reservations about recommending the use of this charming book as an unorthodox introductory textbook for undergraduates. Indeed, W. H. Freeman, Inc. has recently brought out a soft-covered one-volume student edition of the book. Most of the topics which an introduction to cell biology should include are touched on and usually developed in reasonable depth. A short history of the subject is included. Basic techniques that are discussed, often with accompanying diagrams, include cell fractionation by differential centrifugation, chromatography, gel electrophoresis, and autoradiography. The text includes a selection of beautiful light, scanning electron, and transmission electron micrographs. Metabolic diagrams are clear and are made more effective by the use of color. Basic current concerns are treated, amongst them: genetic manipulation and biotechnology, natural gene splicing in the generation of immunoglobulin diversity, proto-oncogenes and the cellular initiation of cancer, the chemiosmotic model, the origin of life, the endosymbiotic hypothesis of the origin of eukaryotes, and phylogenetic reconstruction by molecular sequencing. Bioenergetics is considered whenever appropriate, and processes are characterized by their free energy changes. Appendices provide important supplementary information on bioenergetic principles and on classes of biomolecules. Indeed, the only major problem that I see with the use of this book as a textbook is the complete lack of references. Even the lay readers would probably wish to follow up topics that enchant them, and student readers would find a bibliography especially valuable.

In summary, *A Guided Tour of the Living Cell* is a unique, charming and effective introduction to the eukaryotic cell and to the delightful mind of one of the major figures in modern cell biology.

Ira N. Feit
Franklin and Marshall College

Table of Contents

Computer-Based Education in the Biomedical Sciences
Introduction

It is virtually impossible to go about your daily business today without coming into contact with a computer. Even if you do not work with them directly, you will encounter then at the bank, your local retailer, your physician's office and everywhere else that handles large volumes of information or money.

The classrooms of our schools are no exception. At every level of the educational ladder, from kindergarten to professional schools, teachers and students are making use of the computer in a variety of ways.

This process began in the '60s when most educational institutions got their first mainframe computer. Some short time after the first computerized payroll check appeared, or the first batch-processed statistical analysis of an experiment was picked up, someone decided that the if the computer could do "all that" it obviously could do something to make teaching better.

That initial optimism did not last very long at most schools. Computer-based educational materials were designed, tested, and in some cases, even used by students. But the requirements of working with centralized, time-shared mainframe computers proved too constraining, and by the middle '70s computer-based education seemed destined to remain of "academic" interest to a small group of computer scientists, and educational and cognitive psychologists.

In 1978 the first demonstrations of personal computer-based educational programs occurred at the FAll APS meeting in St. Louis. Since then the number of such demonstrations, as well as workshops and symposia, has grown tremendously. We are in the midst of a true revolution in teaching, one based on the power, low cost and accessibility of the personal computer. The symposium "Computer-Based Education in the Biomedical Sciences" and the displays at the Learning Resource Center at the 69th Annual Meeting of FASEB in Anaheim presented vivid and exciting evidence of this.

The history behind the organization of the symposium will serve to illustrate some of the developments mentioned above. In 1983 the Education Committee of the American Physiological Society sponsored a workshop at the FASEB meeting in Chicago at which 30 or 40 of us discussed developments in computer-based education (CBE) in physiology. These discussions, and the results of a more extensive mail survey that we conducted at that time, documented what those of us who had organized the workshop had suspected; there were a large number of physiologists writing computer programs to teach something to someone. It was also clear that this effort was, and still is, being carried out like a "cottage industry"; that is, there is little national "advertizing", no national "market", and few of us know what our colleagues down the street or across town are doing.

The following year, at the '84 FASEB meeting in St. Louis, the Education Com-Committee sponsored a second workshop, this one formatted to give the novice at CBE some "hands on" experience with the technique. For this workshop we deliberately sought participation from members of all of the FASEB constituent socieites, and we found a great deal of interest in CBE in all of the biomedical disciplines. We had almost twice as many applicants as we could accommodate, and, to our surprise, over half of the participants were non-physiologists.

It seems clear that the time is ripe for those interested in CBE in all disciplines to begin talking to one another, sharing common problems, and hopefully common solutions.

The first set of papers that follows is the proceedings of the symposium "Computer-Based Education in the Biomedical Sciences". In organizing the symposium I attempted to bring together as diverse a roster as possible, and papers were presented describing CBE applications in all of the bioscience areas. In addition, several speakers addressed some exciting new developments that are occurring and that will substantially alter all CBE activities in the future.

The second set of papers are contributed by individuals who had CBE exhibits in the Learning Resource Center. While no central planning had gone into that "program", the number and diversity of the exhibits attests to the level of interest in CBE.

My sincere thanks to my colleagues Allen Rovick and Harold Modell for their advice during the months of organizing both the symposium and the publication of these papers. Glenda Keaton was again remarkably patient with our efforts to get our manuscripts into camera-ready format.

Joel A. Michael

USE OF COMPUTERS IN THE TEACHING OF PHARMACOLOGY, TOXICOLOGY AND THERAPEUTICS

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We have been using computer aided instruction (CAI) for the past 12 years. The system is used each year to teach 200 medical students, 120 nursing students, 36 graduate students and approx. 30-150 practicing physicians. Students are evaluated by a computer-based, multiple choice examination system (CMI), which contains some learning synthesis questions in addition to the usual content. There are 177 lessons which are approximately 20-45 min. running time. The entire system is supported by a large mainframe IBM computer using Phoenix. At least 15% of our medical students get their course work on their home computers by telephone. We have recently been able to transfer the course material from the IBM to microcomputers. Thus, we are able to offer the system to users who do not have access to a large mainframe IBM but do have access to microcomputers. They are available on microprocessors that have a CP/M disk operating system. At the present time the material is made available to various schools under the CATS Consortium. This is a loosely bound, not for profit group sharing teaching material.

The purpose of this paper is to describe the use of a computer-assisted teaching system (CATS) for teaching pharmacology to health professionals. The CATS is composed of two parts: computer-assisted instruction (CAI) and computer-managed instruction (CMI). A consortium of CATS users was established in 1974 to share the philosophy and teaching material of the CATS, and 65 domestic and foreign schools are currently members of the CATS Consortium (1).

Objectives

Five major objectives were identified as being essential for a teaching program:

1. Pharmacology courses must be easily available at any time throughout the year to students.

2. Programs must be able to handle students with different levels of preparation.

3. Students must be able to progress through the course at varying speeds (self-paced).

4. The system must provide for frequent and rapid feedback to both the student and instructors.

5. The teaching program should utilize newer educational technology and techniques to provide optimal flexibility.

To meet these objectives, a modified "Keller Plan" was adopted, and the pharmacology course was organized into modules (2). Students were required to demonstrate competence in each module or unit.

It is apparent that the teaching philosophy followed by the program cannot be provided by a conventional approach. There were two basic ingredients needed to adopt the philosophy successfully, namely, a large question bank file from which multiple examinations of equal difficulty could be generated and multiple sources of information available to the students. It was for these reasons that computers were introduced into the pharmacology teaching program, and extensive effort was put forth toward the development of CAI and CMI. The CATS is used to teach basic pharmacology to different groups of health professional students. The courses offered include medical pharmacology, nursing pharmacology, and two series of independent study courses through the graduate school.

CAI consists of 177 teaching programs; they are of four basic types: (a) self-instruction, (b) case histories, (c) review question programs, and (d) laboratory exercises. The self-instruction programs are similar to programmed texts in that the computer presents text or didactic information and then asks the students a series of questions. Each program is usually equivalent to a lecture on a single topic. The format of these programs may include simple to very complex branching decisions. Some of these programs include a pretest and posttest that can be used to evaluate their effectiveness.

The case history, or simulated patient encounter, consists primarily of problem-solving exercises. Although the general format is the same as in the self-instructional programs, the cases use more sophisticated logic and permit greater flexibility in response. For example, in a toxicology case, the student can lose a patient in six ways but can save him in only one. The major difference between this computer simulation and the actual emergency room situation is that the students who lose the patient are given a second chance to save him by the computer.

In the review question programs, the logic is relatively simple (question → response → text → question → response → text). There is little or no branching, but the computer does keep track of the students' performance and gives them a score at the end. These are drill-and-practice-type programs.

In the laboratory exercises cat blood pressure is studied using simple graphics. There are exercises in autonomic drugs. There are also laboratories where a student must identify an unknown drug using known antagonists and agonists to logically deduce the answer. These are very popular with students.

From the Symposium Computer-Based Education in the Biomedical Sciences presented by the American Physiological Society at the 69th Annual Meeting of the Federation of American Societies for Experimental Biology, Anaheim, California, April 25 and 26, 1985.

Table I illustrates the table of contents of one of our units. There are a total of seven units (Table II) and we also present examinations and Chemquest. The latter is a chemotherapy question system in which the student uses the computer to find the data to answer the question posed.

TABLE I

Courses in the ANS Unit Include:

01 Augonomics I: General
02 Autonomics II: Neurotransmitters
03 Autonomics III: Cholinergics
04 Autonomics IV: Adrenergics
05 Autonomics V: Review Questions
06 Case: Unexpected Drug Reaction
07 Autonomic Drug Matching Quiz
08 ANS Review Questions
09 Arterial Blood Pressure in the Anesthetized Dog
10 Myasthenia Gravis and Drugs that Affect Neuromuscular Junction
38 Reversible Obstructive Lung Diseases
39 Case Study: Asthma
40 Drugs Used in Treatment of Asthma
47 Peptic Ulcer
90 ANS Exam

80 Series
80 ANS General Principles
81 Cholinesterase
82 Muscarinic Agents
83 Nicotinic Agents
84 Neuromuscular Agents
85 Catecholamines
86 Alpha-Adrenergics
87 Beta-Adrenergics
71 Laboratory Exercise I
72 Laboratory Exercise 2
73 Laboratory Exercise 3
74 Laboratory Exercise 4
75 Ophthalmology
91 Pharmacologie du Systeme Nerveaux Autonome I
92 Farmacologia del Sistema Nervioio Autonomo I
93 Cholinerge Mechanismen und Anwendungen

Please enter the two-digit number of the course you would like to run.

TABLE II

The units available in PHARM are:

GEN--general principles
ANS--autonomics
CVR--cardiovascular
CNS--central nervous system
CHEMO--chemotherapy
TOX--toxicology
BLEND--blood drugs and endocrinology

TO SEE FORMAT FOR ANSWERING QUESTIONS, TYPE THE WORD type THEN PRESS "ENTER" WHEN USING REVIEW QUESTIONS OR SAMPLE EXAMS.

EXAM--FOUR FINAL EXAMS are available for study

Please enter unit you wish to run.

Initially all CAI programs were written by staff members in their area of expertise. Today many of the programs are written by medical students with varying amounts of faculty consultation. The students' experience as users of the programs enables them to write programs that are very efficient in teaching. This experience also meets their obligation for a communication skill requirement.

The use by students of the four types of programs depends somewhat on their level of training. Medical students in pharmacology often use the self-instruction programs early in their study of the unit material and use the review question programs just prior to taking the unit examination. The case histories are most frequently used by members of the housestaff and by practicing physicians. Since all of the CAI programs were initially designed to be used by second-year medical students, it was anticipated that these programs would not be effective for teaching graduate students, nursing students, and other health professionals. However, experience shows that this is not the case and that the majority of the programs can be used effectively by any group of health professionals. More than 95 percent of the medical and nursing students use CAI to study pharmacology (3).

Hardware

The entire system is supported by a large mainframe IBM computer using Phoenix as an operating system. It can also run on a DEC-10 in the Pilot language. Some parts run on a CDC/Plato using Tutor. It can also run on an Amdahl computer. The course offering on the IBM is current, some of the others are somewhat dated and they are not recommended by the Consortium. The original language was Coursewriter III. It can also run on other IBM systems; however, this is done only by our Consortium members overseas since those IBM systems are not available on the domestic market.

The students can obtain the course on an IBM 3270 or similar IBM terminal. It can also be obtained on other terminals compatible with IBM or on any TTY. The latter is obtained by a simple telephone modem connection to the main computer. Some 20-25 of our medical students and a few graduate students get their course work on their home computers by telephone. Some of the graduate students have obtained their material using long distance, low cost telephone lines. This is especially true of MS candidates in Nursing, who also hold down professional positions in community hospitals that are 200 miles away from our Center.

The CMI system is written in COBOL and thus is intelligible to all large computers that have a COBOL compiler. The test question bank (11,000 questions) is revised every three years by a national committee of CAT Consortium members. The grading portion of CMI is via BASIC programs and operates on microprocessors linked to a Chatsworth reader. Development is under way to make the complete test bank available to operate on microprocessors. We have recently been able to transfer the course material from the IBM mainframe to microprocessors. This is done by a text transfer to an 8-inch disk. The latter can be converted to a 5-1/4 inch floppy disk that can be run on almost any microcomputer which has a CP/M disk operating system. Thus, we shall be able to offer the system to users who do not have access to a large mainframe IBM but do have access to microcomputers. The system can thus be operated by microprocessors like Kaypro, Radio Shack and similar machines but not Apple. We are also developing these programs on a hard disk (Winchester). In addition, we now

can supply these courses on an IBM-PC. This is written in TURBO-PASCAL and can also be used by IBM-type compatible microprocessors like Zenith, Columbian, etc.

The most thorough evaluation of the CATS was by Project MEDSURVEY, a project undertaken by the Human Resources Research Organization (HumRRO) for the National Library of Medicine to seek answers to specific questions about the nature of CAI development in medical schools (4). The report focused on the experience of eight medical schools that were developing CAI as a teaching tool for biomedical sciences, and a major part of the study involved an evaluation of the CATS. One question asked: does CAI improve student performance? From the 1975 class of 159 third-year medical students, 86 were selected to participate in a survey. Participants were evenly divided into two categories, 43 high CAI users and 43 low users. Since the department-assigned grades were superior, satisfactory, or unsatisfactory, the HumRRO committee arbitrarily assigned letter grades based on the total number of points accumulated by the students in the course. Results showed that grade performance of high users was significantly better using a two-sample Kolmogorov-Smirnov Test. The greatest impact was on the reduction of C grades and the increase in B grades. The number of tests taken per unit for the two groups was not different. These results seemed even more impressive when it was found that the aptitudes of the high users were less than of the low users based on Medical College Admission Test scores as well as cumulative grade-point averages.

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A ROLE FOR CLINICAL CASE SIMULATIONS IN BASIC MEDICAL SCIENCE EDUCATION

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Simulations may be used in basic science education to illustrate principles and concepts operating in events which, for various reasons, are unsuited for direct real-life involvement by students. Also, in some medical schools senior students and internes have access to simulations of clinical cases which allow them to test and improve their diagnostic and management skills. The simulations described here serve yet another purpose: they provide students, during the first year of their professional training, an opportunity to apply basic science knowledge, which they are acquiring concurrently, to the identification and management of the physiologic, metabolic and/or anatomic problem(s) underlying the signs and symptoms of a specific "patient". In spite of their settings these case studies are not meant as an introduction to clinical medicine. Rather, they attempt to strengthen general problem solving skills by presenting a series of challenging interactions in a way that engages the students' commitment to identifying the underlying problem and to deciding upon appropriate treatment. This is done in settings consistent with their anticipated future role as a doctor. However, it is clear from the context in which the problems are presented that, while learning to apply basic concepts in what are perceived as realistic clinical situations, the users are also testing their ability to recall essential basic science facts and principles and are being given the opportunity to correct misconceptions.

Designing a Simulation

The considerations that entered into the planning and production of the present case studies were based on experience with the use of latent-image-on-paper (1) and microcomputer-based simulations (2-4) in a medical biochemistry course that emphasizes problem based learning (5,8). Many of the same principles of educational software planning and production described here are employed by others (9).

Since students in most medical schools are already recieving massive amounts of factual material, it was decided that the purpose of the present simulations should be to strengthen prob-lem solving skills rather than to provide additional information to be remembered. In this context, problem solving was defined as the process whereby a student detects and analyzes a new, unfamiliar problem and then determines how it is to be managed. From this it might be expected that the instructor's role would be limited to designing the case study and to giving assistance to the learners only through programmed replies to their responses during the simulation. In practice, the nature of student encounters with the programs often leads to mutually enlightening discussions with the designer-instructor.

Although medical students are understandably enthusiastic about the quasi-clinical settings, they are also aware of the necessity of remembering facts and concepts for examinations. The novelty of the medical setting does not distract them from appreciating the importance of the basic knowledge needed to understand the underlying pathophysiological processes. Indeed, being able to recognize the place of an otherwise isolated abstract fact in a coherent conceptual framework seems to favour its retention in long term memory. Examination results also show that information-processing skills learned while using basic science knowledge to diagnose a "patient's" problem can be transfered to analogous new situations.

The programs are designed to encourage students to employ diagnostic patterns favoured by competent physicians (6,7). Rather than requiring the exhaus- tive gathering of data before beginning its evaluation, users are influenced to integrate each piece of information, as it is encountered, into their knowledge base and to generate and continually revise appropriate causal hypotheses. Although it is not required that explicit hypotheses be typed in, rhetorical questions inserted at crucial points as the "story" develops imply that it would be helpful to have a coherent explanatory scheme for the findings. Each of the simulations is constructed around a basic plan: a series of sections, each consisting of an information gathering step, followed by one or more questions that explore the student's understanding of that information. Most information is presented in the idiom that might be used by a patient, the "doctor" and her/his colleagues. However, information that is better understood visually appears in graphics which can be made to respond dynamically to student input. Approval is expressed for correct responses to questions; incorrect or inappropriate answers elicit progressively more explicit and helpful feedback. The user thus leaves each section with an understanding of its informational content and the significance of the questions and their answers. Following a number of sections a summary of findings up to that point is shown. Repeated encounters with these sequences of information gathering steps, formative questioning and brief reviews encourages continual revision of

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the current working hypotheses as the student progresses through the simulation.

To a considerable degree the effectiveness of clinical simulations as a learning medium is dependent on having the student accept the role of the "doctor" responsible for detecting the patient's problem, identifying it and managing it therapeutically. Acceptance of such role playing is encouraged, beginning in the Opening Scene which might, for example, state: "You are now in family practice in Gofuhrkroch, Alberta." It can be sustained by permitting some freedom in selecting the order in which specific diagnostic approaches are explored. Such branching, although limited by the program, gives the illusion of choice and aids in having the student accept the role of problem solver. The strong intrinsic motivation associated with this implicit fantasy role is sometimes difficult to maintain because of the user's lack of clinical experience. This may be mitigated by not requiring that diagnoses be phrased in conventional medical terms. Rather, s/he is asked to identify the underlying mechanism in terms of disturbed physiology, biochemistry, and/or anatomy. Similarly, acceptable therapeutic measures are those which, at the current level of the students' knowledge, are appropriate for the underlying disturbance. To sustain a measure of realism, therapeutic errors are shown to aggravate the "illness" and in two simulations, threaten the life of the "patient". At intervals during the study the student may seek the advice of a senior "colleague" or that of consultants. This may or may not prove useful but the "doctor" invariably is left to make the diagnostic and therapuetic decisions. These can be difficult since the program may demand a decision be made before an obsessive information gatherer has been able to satisfy his/her need for certainty.

The intellectual exercise of applying basic science facts and concepts is imbedded in these case studies in situations that may become emotionally loaded. This may vary from transient frustration to exhaltation, depending on the user's success in dealing with the problems posed. Frustrations of students who have difficulties, either through lack of basic knowledge at the beginning of the simulation, or because they are less able as problem solvers, are relieved by providing (eventually) the expected responses and explanations, as described above. This design thus represents an attempt to replace the usual external motivation of future examinations with the intrinsic motivation associated with success in a task that is both intellectually satisfying and congruent with an anticipated future role as a physician. These design components may favour long term retention of information and information-processing (problem solving) skills.

It is important that students not be distracted by the mechanics of operating the computer. To minimize this the simulations are offered on Apple II computers, machines that are not physically intimidating and can be used without learning the arcane jargon of main frame access. In the first screenload the student is told that pressing the Return key will control the speed of movement through the exercise - and the location of the Return key on the keyboard is described. Next, by touching the "Y" or "N" key the user can choose to view or omit a set of instructions common to all the case studies. In the instructions the various kinds of responses which will be requested later are explained, and the way to correct spelling errors made during entry of responses is described. The significance of the rhetorical questions mentioned above is explained and a few minor points of advice on pacing, keeping notes, etc. are given before the program returns to the simulation proper.

Users are made more comfortable by assuming few keyboard skills and by introducing gradually the more unfamiliar response modes which will be required of them later. Thus, after a few screenloads of information describing the "patient" have been shown, the first opportunity to select information appears as a multiple choice question. Although a physician is rarely faced in real life with a choice in this format, it is the one with which most students are familiar and therefore, most comfortable. After a few such information-gathering and questioning sections the user is introduced to entering words or phrases on the keyboard to indicate a decision: s/he is asked to choose one of several words seen on the screen and to type it in. Later, once the basic facts and concepts needed to begin understanding the "patient's" condition have been encountered the kind of questioning changes again. The student is now asked to enter a word or phrase, without the help of cues inherent in the earlier types of questions. Somewhat disconcerting initially, the "Type in your answer" now being reuested requires recall of appropriate cognate information from the student's long term memory into her/his working memory. There it can be integrated with the incoming information to solve the immediate problem raised by the program's question. Research in medical problem solving indicates that this is the way physicians operate in real-life problem solving situations (6,7). Although this is obviously a more realistic way of eliciting a response, it is also technically more difficult to employ successfully as it requires a good understanding of the various student repsonses to be expected. On large mainframe computers this "free language" format is limited only by the imagination of the designer. However, because it consumes large amounts of disk space it cannot be used as extensively as might be desired in programs running on most microcomputers.

Production of Simulations

Aside from the selection of Apple II computers for programming and student use, the single most effective decision made in planning the production of the present simulations was the choice of PILOT as the programming language. In the Apple Super-PILOT version, PILOT has most of the features of a fully developed language, USCD Pascal, upon which it is based. However, because PILOT was designed specifically for the production of question-and-answer teaching/learning materials, beginners can rapidly mount a trial exercise. This has enabled computer-naive colleagues to try their hand at programming learning materials with little threat of failure. Few have persisted with programming but from the experience they have learned enough of the peculiarities of the computer medium to help them in designing more effective exercises and in transmitting their ideas more clearly to programmers.

Because each simulation requires from 300 - 600 hours of work from its conception until final debugging is completed, it soon became apparent that the tasks of designing, programming and testing would need to be divided among the members of a small, informal team of instructors and medical students. Time constraints and differences in content knowledge, commitment and technical skill in designing and programming have determined the changing patterns of task sharing. Currently, a computer-naive instructor may recieve help to select from the literature or hospital records a clinical case that suits his educational purposes. The learning objectives of the exercise are next identified. This may be troublesome initially since, for a simulation to be effective, the objectives must be behavioral, i.e. not so much what the student should KNOW, but what s/he should have learned to DO at specific points in the exercise. These objectives and substantive material from the case description are next incorporated into a tentative flowchart and a trial version of the exercise is programmed, usually by a medical student. This and the objectives are reviewed and revised repeatedly by the instructor, design advisor and programmer until the product is ready for testing on the intended student audience. In this cyclic task the roles of the participants often change and medical students on occasion have assumed all three roles.

The advantages of the team approach in terms of cost and consistency of product quality in software production are well established (9). In the present context, successive cycles of fine tuning a case study to the knowledge levels, personal objectives and colloquial idiom of the intended audience were greatly facilitated by the involvement of students in the designing and programming. Interactions between faculty member content-experts and student designer-programmers have repeatedly proved to be pleasant, mutually beneficial learning experiences.

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USING COMPUTER-ASSISTED INSTRUCTION TO TEACH NUTRITION

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ABSTRACT

A 15-week introductory course in nutrition was developed into a computerized study guide or "autotutorial" program. There are 1,950 statements and review questions on main-frame or microcomputers that are used by students to preview or review lectures, or study for exams. The program has been highly accepted. Over two years, only 3% of 352 users found it unacceptable. Based both on students' perceptions and actual analysis of grades, users' grades in the course were significantly higher than those of nonusers, averaging about +5 points. Students reported the program highly advantageous for testing comprehension, reviewing and reinforcing lectures, improving their concentration, adding enjoyment and interest to studying, and improving their spelling. Students did not find the program particularly tedious or boring, and spent on the average 17.5 hours using it during the semester. The principle disadvantage of this type of computer-assisted instruction is the large amount of time required to develop it -- at least 2,000 hours.

INTRODUCTION

Computer-assisted instruction (CAI) has been used for over a decade in a variety of scientific disciplines, and evaluation of it generally has been favorable (1,2). If used wisely, computers offer unlimited opportunity to improve and enhance learning by students at all levels including university. Currently, the most effective role of computers is in supplementing good teaching, not replacing it (3).

Although a variety of software programs exist for the teaching of nutrition (see the Journal of Nutrition Education, June 1984, for an extensive catalog of these programs), they address primarily diet analysis, health education, and limited segments of basic nutrition. Apparently little has been published about the use of CAI to accompany entire courses in introductory nutrition. We developed and evaluated a computerized autotutorial program (or study guide) to accompany a 15-week, semester-long course in the fundamentals of nutrition. It would be suitable for use along with the first course in nutrition taken by college-level students or advanced high school students who have had an introduction to biology and chemistry.

THE PROGRAM

The content of this program was based on the lecture notes used in an introductory science course taught by the senior author on the Fundamentals of Nutrition. The main points of the lecture were developed into 1,950 statements or objective questions that emphasized the most important information in the course, and which could be used by students to review or clarify lectures, to prepare for exams, or even to preview upcoming lectures. We refer to this program as "autotutorial," because students can work entirely apart from instructors in learning the information, to the point that the whole course can be completed on the computer with no instruction, although we have not evaluated it extensively in this mode. The students in the lecture course have used this program almost entirely from over 100 remote terminals located on campus and attached to the university's DEC-2060 main-frame computer.

There are three main components to the program: (1) the text files, which contain the nutrition information from the course; (2) a "driver program" which is a set of computer instructions, written in FORTRAN, that runs the entire CAI program; and (3) the command files, which initiate the "driver program." The categories of topics in the text files are: history, senses and appetite, digestion, carbohydrates, lipids, protein, metabolism, energy, vitamins, and minerals. An extensive example of our program has been presented elsewhere (4).

To use this program, the only instructions the student needs are how to turn on the remote terminals and how to log into a personal account they are given (64K bytes permanent and 192K bytes temporary disk space). With a single command the program becomes entirely interactive with the student. Very short instructions are given within the computer program that tell the student how to quit, how to move backward or forward with complete flexibility, or how to send comments to the instructor for later reply. In conjunction with this program, the students are given 4 written pages of instruction on how to use the computer and the program. We also give a one-hour lecture on the use of our program and the terminals, but only 20% of the students attend; about one-half of the users of the program have indicated that they need no instruction at all to use it quickly and easily.

EVALUATION

The nutrition course involved is intended primarily for freshmen and sophomores at the University of Vermont. It is a prerequisite for students majoring in animal sciences and human nutrition, but is used by health and biology majors, preprofessional students, and many others interested in an introduction to nutrition. It is taught each semester to a single class of about 250 students.

At the end of each of four semesters during 1983-84, a questionnaire was handed out to a total of 1,002 students in the course and 352 replies by users were received. Although about 80% of the students in class signed up for this optional

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project, not all pursued it, primarily due to lack of sufficient remote terminals on campus. Next to the introductory computer science course, students in this nutrition course are the heaviest users of the main-frame computer on campus.

The following results were obtained in response to the questionnaire:

TABLE 1. How Useful Was the Program?

	Percent Response			
	Spring 1983	Fall 1983	Spring 1984	Fall 1984
Very useful	51	57	74	63
Useful	39	34	22	27
Somewhat useful	7	9	4	7
Not useful	3	0	0	3
n	(73)	(121)	(91)	(67)

Since over 95% consistently thought the program was useful, we concluded that the effort in developing the program was worthwhile.

Of greatest importance was whether or not this approach improved learning. We chose to use the course grade to judge this. At the end of each semester but before students received their course grade, we asked them their perception of the effect of using this program on their grade.

TABLE 2. Students' Own Perceptions of the Effect of the Autotutorial Program on Their Grade

	Percent Response			
Grade change	Spring 1983	Fall 1983	Spring 1984	Fall 1984
+ 7-9	21	29	30	27
+ 4-6	41	38	50	43
+ 1-3	21	23	15	21
0	15	8	4	6
minus	1	2	1	2

That so many students thought use of the "autotutorial" program had a substantial beneficial effect on their grades was rather surprising. However, the results were fairly consistent over the four semesters. We were pleased with the low number of apparently disgruntled students. The students' perceptions of an increase in their grades were confirmed by actual analysis of the course grades of users versus nonusers of the computer program.

TABLE 3. Course Grades of Users vs. Nonusers

	Spring 1983	Fall 1983	Spring 1984	Fall 1984
Users	81.3	82.2	83.4	83.0
n =	(72)	(121)	(91)	(67)
Nonusers	76.2	76.9	78.0	77.8
n =	(196)	(130)	(134)	(191)
	p<0.001	p<0.001	p<0.001	p<0.001

Throughout the four semesters, the users consistently achieved about a 5-point higher grade in the course. Therefore, there is excellent agreement between the beneficial effects of the program on course grades as perceived by the students and what actually happened to them. Nevertheless, these results must be interpreted with great caution since the class had not been divided into equalized test and control groups. The project was optional; any student was free to volunteer or not for the project. Whether there was a bias or selection for users to be students with a higher potential for good grades, we don't know.

However, we did run several correlations using the grade point average (GPA) the students had when they entered the course or the course grades, versus several of the other questions asked. These are shown below and the probability level for significance was set at .05 (NS = not significant). For the non-parametric data, Kendall's Correlation was used.

TABLE 4. Correlation Statistics with Users

	Spring 1983	Fall 1983	Spring 1984	Fall 1984
GPA vs grade	-	p<.001	p<.001	p<.001
GPA vs perception of grade	NS	NS	NS	p=.055
GPA vs time at computer	NS	NS	NS	NS
Actual grade vs perception of grade	-	NS	p=.008	p=.009
Actual grade vs time at computer	-	NS	NS	p=.009
Perception of grade vs useful	p<.001	p<.001	p<.002	p<.001
Actual grade vs useful	-	NS	p=.017	p=.03

All significant correlations were positive; no significant negative correlations were found. As expected, the students with the higher GPAs achieved the higher grades in the course. However, there was little evidence that the students' university standings were related to their perception of the effect of the autotutorial program on their grade (only one borderline significant correlation out of four semesters), and definitely no correlation between their GPA and time spent at the computer. Apparently, neither the students with higher grades as a group, nor those with lower grades, tended to spend more or less time than the other working on this program. In two of the three semesters studied, there was a significant positive correlation between actual grades and the perception of how much the grade would increase. That is, the students with the higher grades perceived that their grades would be higher. But there was only one significant correlation between their grades and time spent at the computer program. The last two lines of Table 4 show strong relationships between the students' perception of their grades or the actual grade and how useful the program seemed to be. We conclude from these data that our autotutorial program was perceived by the students as being very useful in enhancing their knowledge in the course (judged by grades) and in actually increasing their grades. But these benefits were not well correlated with time spent at the computer.

The advantages and disadvantages of the autotutorial program as judged by the 352 student users are shown in Table 5.

TABLE 5. Advantages and Disadvantages

	Percent Response			
	Strongly agree	Agree	Disagree	Strongly disagree
Advantages				
Reviewed lectures	67	31	2	0
Reinforced lectures	73	26	1	0
Was fun and interesting	41	51	8	0
Helped with spelling	56	35	7	2
Available anytime	20	40	34	5
Could set own pace	68	30	2	0
Increased concentration	44	48	7	0
Tested comprehension	49	46	5	1
Disadvantages				
No human interaction	4	26	54	17
Tedious and boring	1	14	58	27
Program incomplete	4	17	57	23
Takes too much time	2	17	60	21
Didn't know how to use	3	11	58	29
Terminals unavailable	11	42	40	7

The original intent of developing the program to review and reinforce lectures was easily met. Most students found the program fun to use without being boring. Part of the success here undoubtedly relates to the fact that this program is being used in conjunction with a lecture course. We did not observe any reduction in classroom attendance due to institution of the computer program. The lectures are considered to be dynamic and interesting, and are replete with visual aids, which may account for continued attendance. It was important to find out that students highly agreed that their ability to concentrate on the material and to test their own comprehension was improved. Entering university students often have serious problems on these two points, especially if they study alone or are unable to devise systems to use with solitary studying. The autotutorial program helps with this. The principal weakness of the computerized approach to studying was the unavailability of terminals. Like many universities, we lag in keeping up with the rapidly increasing demand placed on our main-frame computer. Conversion of the program to microcomputer disks, which we will accomplish this year, will help resolve this problem. Part of our entering freshmen class is now required to buy microcomputers for classwork.

THE FUTURE

Programs like ours, undoubtedly, will be modified and adapted in the future to a variety of other computerized educational approaches. Three that we are working on are the following. First, we will use this program on microcomputers in outlying regions of Vermont as a stand-alone course where there is demand for such a course but no one to teach it. Students would use the program in conjunction with a text, but with no, or infrequent, visits by an instructor. We have not evaluated this approach, but very limited use of it suggests that it will be very successful. However, the lack of human interaction will be a very negative factor. Second, we have built a "test-generator" to accompany this program so students can take multiple-choice exams directly from the computer with no hard copy generated. The main problem is figuring ways to maintain security during examinations. Third, by use of interactive video, we plan to incorporate pictures, from the 300-400 slides used in the course, into the autotutorial program. This will greatly increase the value of the program if used as a stand-alone course, and also allow students time to review the slides shown in class.

SUMMARY

The concept presented here is a computerized autotutorial workbook to cover an entire semester-long course in nutrition. Students find it highly useful, easy to adapt to, and valuable for improving their study habits and testing their knowledge. Students perceive that their grades are improved by use of this program, and this is corroborated by actual grade comparisons. Our experiences with this autotutorial program over four semesters have been highly positive. The main disadvantage to development of such programs is the large amount of professional time required, which may be at least 2,000 hours.

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APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN EDUCATION--- A PERSONAL VIEW

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Abstract

The potential of the computer in education has hardly been realized. However, there has been progress in several key areas. Computer hardware is steadily decreasing in price. Computers suitable for education will shortly have advanced graphics capabilities and enough speed and memory to run Artificial Intelligence (AI) programs. These programs explicitly represent knowledge about a subject or skill and can automatically generate problems and evaluate student's answers even in complex domains such as diagnosis. AI theories may also help us understand expert problem solving, learning and teaching. In addition, there has been other interesting work in computer education that can be integrated with AI methods. If a picture is worth a thousand words and doing is understanding, then computer graphics and interactive video should provide us with a great deal of leverage in instructional applications. Viewing the computer as a unique medium that may allow us to teach knowledge differently is an exciting opportunity. Additionally, the computer is a communications device that may allow us to retrieve and annotate encyclopedic knowledge that is presented in a new form that includes animation, interaction, and feedback.

Introduction

There is little doubt that computers have not yet had the kind of broad and dramatic impact on education that some people believe is possible. They have neither revolutionized learning nor solved pressing educational problems that face society. Perhaps it is far easier to see the potential of computers in education than it is to realize that potential. First of all, education is an extremely complex endeavor. It is intertwined with political, economic, and social concerns. Education, in the fullest sense of the word, can occur anywhere and at anytime. But even the interaction between a teacher and one or more students in a formal setting is extremely complex. We still understand very little about the process of transmitting knowledge or skills and the process of learning. Secondly, programming is a very complex endeavor. It can take several man-years to produce a sophisticated program. The age of computer software is still in its infancy. Thirdly, powerful computers (e.g., lisp machine) are still too expensive for most schools or individuals to purchase. However, this technological bottleneck should be the first to break as computer hardware continues to drop in cost at a fantastic rate. The potential market for home and school computers is enormous. Soon we may be able to mass-produce very inexpensive computers that are both very fast and very small. However, there is still another factor which may be the most important of all. This fourth factor can be called the 'Poetry Principle' as Seymour Papert referred to it in a talk many years ago. (PAPERT76) In order to proceed, we should have a vision of what we want education to be and what we want computers to be like. Papert's vision of education is concerned with how the child and the culture as a whole relates to intellectual subjects (e.g., mathematics). The future is yet to be shaped and, undoubtedbly, there are alternatives.

Why Artificial Intelligence?

Artificial Intelligence (AI) can advance education in two broad ways: (1) provide the basis for smarter, friendlier and more responsive computer programs, and (2) provide a more formal understanding of the process of teaching and learning. The second endeavor is often associated with Cognitive Science, a field which is closely related to AI, that seeks to understand human cognitive processes. As a result, such an understanding can impact education even when a computer is not used. Although the techniques that AI programs use do not necessarily have to correspond to human methods, AI practioners in the area of computer-based instruction are often inclined to believe that programs will be more effective if they are based on human methods of problem-solving, learning, and teaching.

Does the future of software lie in AI?

This is a difficult question to answer because it's hard to predict the progress that will occur in the AI field. It seems safe to say that there will be many valuable applications. However, even if AI techniques pervade future software, the AI component will still be integrated with other software technologies. For example, a graphic interface may at times be more appropriate than a natural language interface even if natural language systems advance far beyond their current state. Additionally, traditional numerical techniques will continue to be used when appropriate.

It would be a mistake to view AI as a panacea for educational problems. For example, many agree that there is a need for more individualized instruction, and some may think that a computer could some day replace a human tutor or teacher. But replace in what sense? Can the excitement or emotional warmth that a teacher may transmit to a student be replaced? Do we know to what extent the intellectual functions of a teacher can be replaced? The computer is a unique machine because it can take on so many faces. One can view computer technology as a new medium in which to deliver educational materials.. We can add intelligence to these materials so that they provide feedback or plan instructional activities for students as a coach or tutor might. But I think it would be a mistake to view the potential of the technology entirely in anthropomorphic images. The computer can provide the most leverage if we can integrate its various unique capabilities in a synergistic manner.

Interactive visual imagery and animation hold great promise for educational programs. Two technologies that are currently available are computer graphics and interactive video. These can be used in conjunction with computer-synthesized and natural sound. As the cost of electronic hardware continues to drop, these technologies will become more accessible to increasing numbers of people. Some AI programs already make extensive use of these technologies. For example, STEAMER (STEVENS83, HOLLAN84), an instructional program that is designed to train Navy personnel on the operation of a steam propulsion plant, uses interactive computer graphics to provide a visible and inspectable simulation model of a steam plant's complex physical processes. The graphics are integrated with a mathematical model of a steam plant. AI techniques were used to create a knowledge base that represents the plant's components and the procedures for operating the plant. With the help of an expert steam plant operator, a qualitative simulation of the plant was integrated with the mathematical model and the graphic representations of the plant.

Some AI programs are beginning to use interactive video in cases where computer generated images are inadequate or too costly to provide required imagery. For example, programs that diagnose equipment may ask non-expert users to identify the

visual state of an object or to execute a procedure that is difficult to explain verbally. In some cases, a picture or "movie" sequence can make perfectly clear what words alone cannot.

The roots of intelligent computer assisted instruction (ICAI)

ICAI began with the publication of Carbonell's seminal paper in 1970 (CARBONELL70), in which he delineates the limitations of traditional CAI programs, outlines the basic problems confronting the application of AI to computer-based instruction, and describes SCHOLAR, an ICAI tutor in geography. Carbonell refers to traditional CAI programs as frame-based because they usually present a frame (or screen) of text, ask several questions, and branch to another frame based on the student's answer. (This should not be confused with the popular use of frames in AI, which refers to a knowledge representation formalism, also called a schema.) Frame-based CAI programs require an author to enter complete text passages, questions, correct answers, anticipated incorrect answers, feedback for answers as well as instructions as to where to branch next. These systems are tedious to modify and generally inflexible for a student.

SCHOLAR uses AI knowledge representation and inference techniques to automatically generate questions, evaluate answers, and engage a student in a limited natural language dialogue. SCHOLAR introduced the idea of a mixed-initiative program that allows a student to take the initiative to ask questions. Within its limited domain of South American geography, SCHOLAR could answer many questions posed in English. SCHOLAR's weaknesses include a limited ability to diagnose a student's errors, or more generally, to model a student's knowledge and skills, and an inability to plan significant instructional sequences. Student modeling and instructional planning remain difficult problems today that challenge researchers in AI.

Carbonell outlined the major problems in ICAI, including knowledge representation, inference, student modeling, planning, appropriate feedback, and interaction with the student (e.g., natural language dialogue). SCHOLAR also led directly to work that studied the interaction between a tutor and a student.

Protocol Analysis

Protocols in this context refer to transcripts or other media that represent a record of a problem-solving or teaching session. The analysis of protocols may help us understand more about learning and expert behavior; it is also a method used for building AI programs. For example, WHY (STEVENS77), a program that teaches students about the causal factors influencing rainfall in different geographical regions, was developed by analyzing protocols of tutoring sessions. Protocol analysis has also been used to develop programs that diagnose a student's errors in arithmetic (BURTON82a) and algebra (SLEEMAN82). Protocol analysis can also be used to study expert problem solving behavior. Interviewing experts or students can be a means for collecting protocols or for discussing prior ones with a subject.

Reactive environments --- learning while doing

SOPHIE (BROWN82a), an electronic troubleshooting tutor, emphasizes the idea of providing immediate and relevant feedback to a student working in a problem solving setting (i.e., diagnosing a faulty electronic circuit). Using a clever engineering approach to the problem of natural language understanding, SOPHIE is able to converse with a student in English (including incomplete sentences, pronomial references, etc.) within the domain of diagnosing an electronic circuit. Importantly, the program can respond quickly and handles student input well enough that the interaction can become transparent, allowing the student to focus on the instructional task instead. SOPHIE can evaluate both a student's requests for information and his hypotheses. The program provides relevant feedback, explaining why a student's data requests or hypotheses are or aren't appropriate given the information known at the time. SOPHIE can provide this feedback because it incorporates a computer-based expert that can diagnose circuit faults. A student can observe the computer-based expert solve a problem or choose to participate in the fault diagnosis. Additionally, SOPHIE provides an electronic laboratory which allows a student to introduce a fault into a circuit and explore hypothetical situations. Such experiments in an actual electronic laboratory could be costly or dangerous.

LOGO

LOGO (PAPERT80) has its roots in the work of Piaget, mathematics, and artificial intelligence. It is a computer language, based on a philosophy of education that emphasizes exploration and the testing and debugging of ideas and methods. The most well-known proponent of LOGO is Seymour Papert, one of the original developers of the language and the director of the M.I.T. LOGO Lab throughout the 1970s. In contrast with early ICAI researchers, who attempted to augment traditional instruction or reproduce the behavior of a human tutor, Papert's goal was to offer a new educational vision, based on Piaget's model of children as active builders of their own intellectual structures. Papert's vision depends on providing children with better materials to build with, both physical objects including computers and abstract objects such as models of cognition. Papert believes that the techniques that are used in computer problem-solving can and should be taught to students. In this sense, the student should teach the computer by using an appropriate language to experiment with and to describe a goal behavior. An example is turtle geometry, in which students use commands such as *forward*, *backward*, *right*, and *left* to instruct a 'turtle' to draw patterns on a computer screen.

Turtle geometry is a perfect example of how LOGO's three intellectual roots have been blended. Turtle geometry begins with simple geometric patterns, but can lead the LOGO programmer into complex mathematical concepts. The child can identify with the turtle by relating the turtle's movements to the child's own body moving in space. LOGO allows the student to use problem-solving techniques such as breaking a problem into its subparts. It provides an excellent environment for studying procedures and practicing the debugging of faulty procedures.

Papert has raised much controversy because he challenges the tenets of traditional education, and has been accused of making claims that are difficult to substantiate (particularly the transfer of problem-solving skills from one domain to another). Many educators feel uncomfortable with Papert's lack of regard for formal instruction and curriculum. Some people may agree with both his goals and his criticisms of traditional education, but still have doubts that LOGO programming is a solution. However, Papert views LOGO as a prototypical example and not an end in itself.

Papert believes that students can benefit from thinking about thinking and learning about learning. His philosophy states that mistakes are opportunities, bugs arise naturally, and you can learn from experimenting, recognizing your errors and correcting them. He believes that the gap from the concrete to the abstract can be bridged through the use of transitional objects such as the LOGO turtle. Students can imitate the turtle with their body, imagine it in their mind, or control a floor turtle or a screen turtle (depicted as a triangle) with LOGO commands and procedures. The opportunity exists to reconceptualize domains such as geometry or physics so that that they are more intuitive to learners. Papert suggests computational or turtle geometry as an alternative starting point for a student learning mathematics. Papert has also popularized the idea of microworlds, where students can explore "powerful ideas in mind-size bites." For example, students can explore Newtonian motion in a microworld where objects called dynaturtles can move (even perpetually) in a simulation where friction can be easily adjusted or eliminated.

Student modeling and coaching

An area of general interest in AI is *user modeling* or understanding what a user knows and what a user's goals are. In ICAI programs, this is called *student modeling*. A naive model of a student's knowledge is to assume that it is a subset of the expert's knowledge. This is naive because a student often uses incorrect knowledge as well. Groundbreaking ICAI programs that have a student modeling component include West (BURTON82b), Wumpus (GOLDSTEIN82), and GUIDON (CLANCEY82). West and Wumpus are game environments that include a coach. A coach uses the information in the student model, along with rules about coaching (e.g., when to interrupt), to provide feeback to a student at selective moments. Although these programs model student behavior and provide coaching tips, it is difficult to generalize their methods to other domains.

GUIDON began with the premise that if you have an expert system, a program that solves certain problems at an expert level, then you should be able to teach the knowledge that is encoded in the expert system. GUIDON adds a tutoring component to EMYCIN (VANMELLE81), an expert system shell. GUIDON includes an explicit set of domain-independent tutoring rules to teach a student about the rules in a given EMYCIN knowledge base, most notably, the MYCIN (SHORTLIFFE74) knowledge base for infectious disease diagnosis and anti-microbial therapy. GUIDON is a case-method tutor that includes a student model and uses knowledge about discourse structure to engage a student in a goal-oriented dialogue about a given case.

MYCIN rules combine medical facts with a diagnostic procedure or strategy in an opaque manner. Therefore, many of the rules are difficult to understand, and GUIDON is unable to explain to a student strategic decisions that the program makes implicitly. For example, GUIDON cannot explain to a student that MYCIN is discriminating between two hypotheses because MYCIN did not explicitly follow this common diagnostic strategy. This observation led directly to the development of NEOMYCIN (CLANCEY84), a program that is based on the analysis of interviews and classroom transcripts with expert physicians. NEOMYCIN represents a diagnostic procedure separately from medical facts and rules in such a way that it can be used for multiple purposes, including explanation and student modeling. NEOMYCIN provides the foundation for a new generation of instructional programs that will investigate methods for tutoring students in diagnostic strategies.

A convergence of ideas

The current generation of knowledge-based instructional systems integrate ideas that have their roots in several traditions. In parallel with the ICAI and LOGO research of the 1970s, the Learning Research Group (LRG) at XEROX PARC explored the idea of a dynabook(KAY77, GOLDBERG79), a powerful and notebook size computer with advanced graphics capabilites and a large storage capacity. The first prototype dynabook was a desktop personal computer that included the Smalltalk language and features that are now standard on AI workstations, such as bit-mapped graphics, multiple windows and a mouse. LRG pioneered much of the work in user-interfaces and object-oriented programming that are also used in AI programming environments.

The concept of the dynabook helped shape a view of the computer as a communications device rather than as a computational engine. Earlier work by Englebart (ENGELBART70) provided much of the technology and ideas that LRG expanded on. Even as long ago as 1945, Vanevar Bush (BUSH45) proposed an information and communications device that he called a memex, a desk-size machine that would allow a person to store, retrieve, and manipulate information easily. Bush envisioned the recording or trace of a person's thinking in a data base that can be annotated or examined as an object itself. Recent extensions to these ideas include work on interactive encyclopedias (WEYER84), programming by rehearsal (FINZER84) --- a prototype "programming" environment for curriculum developers that are not trained in traditional computer programming), and several projects underway in the Cognitive and Instructional Sciences Group at XEROX PARC (BROWN82b, BROWN83).

At present, the potential for knowledge-based instructional programs (i.e., programs that use inference techniques acting on knowledge bases) seems greater than ever. Powerful workstations are now available to develop complex programs, and as these machines decrease both in cost and size it will become possible to deliver knowledge-based instructional systems to many people. There is a new enthusiam for developing instructional systems that can integrate knowledge bases, inference engines, bit-mapped graphics, models of problem-solving and learning, and ideas about guided-discovery learning. John Seely Brown, director of Cognitive and Instructional Sciences at XEROX PARC, believes new kinds of learning environments are now possible, environments that change both the form and content of learning, emphasizing process as well as product while allowing students to explore and discover ideas under the guidance of a coach. We can explicitly represent problem-solving methods and exploit interactive graphics to record a trace of a problem-solving session that can be studied as an object itself. In this way, we can *reify* (i.e., make more concrete) the process of problem-solving.

Brown's ideas have directly influenced the direction of the GUIDON project at Stanford, which is in the process of developing new instructional programs using NEOMYCIN as a framework. Currently, NEOMYCIN can diagnose several diseases and provide explanations at both the strategic and domain level. The instructional programs will use a student model and interactive graphics to allow students to observe NEOMYCIN's and their own problem solving behavior, to choose diagnostic strategies, to annotate consultation typescripts (what is the strategic purpose of each question NEOMCYIN asks?), and to debug a faulty diagnosis. These intelligent tools will allow students to explore a computational model of diagnosis in a way that has not been previously possible.

Where do we go from here?

There are enough interesting ideas and challenging problems to keep researchers busy for many years. However, it is now possible to consider delivering AI-based instructional programs in educational settings. Proust (JOHNSON85), a program that diagnoses student's programming bugs for several programming exercises, is being used in introductory programming classes at Yale. However, this is the exception. Most ICAI programs have not been extensively evaluated with students, nor used very much once developed. Because most students do not have access to a mainframe computer, in the past it was difficult to deliver ICAI programs into a classroom environment. Most AI programs are now available on workstations that are small enough to install in a test setting for evaluation. Therefore, it is imperative that developers of ICAI programs begin working more closely with students and teachers to maximize the usefulness of these programs. At Stanford, stronger ties between the GUIDON project and the medical school have been formed that should facilitate this interaction. Such joint efforts between interested individuals should help us more fully realize the educational potential of the computer.

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VIDEODISC - COMPUTER TECHNOLOGY IN THE TEACHING OF PATHOLOGY

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The principle tools currently used in teaching Pathology to medical students are books, lectures and microscopy lab sessions. These are sometimes supplemented by some involvement in the autopsy room but this last accounts for a very small proportion of time spent. The end product of this is (hopefully) a student who can:

a. understand vocabulary.
b. outline the pathogenesis of the major disease process.
c. apply these outlines to disease in specific organ sites.
d. recall disease morphology both macro and microscopic.
e. use laboratory tests in clinical situations.

When considering whether computers would be useful in teaching Pathology it is helpful to assess whether current methods achieve their desired end points and what the costs are in terms of person power, time and dollars.

In an average medical school Pathology occupies about 300 hours of teaching time, most of it in the second year. Perhaps 200 of these hours are occupied by lectures given by one faculty person who spends a mean of 4 to 5 hours per lecture on preparation. Laboratory sessions occupy the balance of time and take 4 to 10 faculty to supervise each session. About half the supervisory staff are residents or unpaid volunteers from affiliated hospitals who spend minimal preparation time. Curriculum meetings, assembling lecture handouts, slide boxes, etc. take, perhaps,a further 300 hours with setting and grading exams (many multiple choice) another 100 hours. The total cost of this effort is an annual outlay of 2000 hours of paid faculty time each year. It is difficult to quantify the time spent in individual student counciling in an informal context, but this is omitted from calculation because it is likely that time thus spent would not be altered by the introduction of computers to the teaching armamentarium.

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Whether these mechanisms achieve success or fail depends on whom one asks. Undoubtedly students are well equipped with facts at the time they take their board exams. Equally undoubtedly, many of the facts are stored in short-term memory and are discarded shortly afterwards to be relearned later or forgotton forever. It seems unlikely that this will ever change since all education prior to practical experience suffers from the same defect. It is only when students have direct personal experience to glue these facts to memory that long term recall is achieved. Thus a certain amount of redundancy is to be anticipated and is probably inevitable.

Is the computer likely to be any more efficient in terms of time and cost in reaching the present end points? Examination of each of the goals outlined above will lead to rather divergent conclusions.

A. Vocabulary

In most schools this is known to be important because many of the questions asked in exams are essentially definitions. However, there is little formal attempt to teach the language of Pathology (too demeaning perhaps?). Yet at this very basic level many students are poorly equipped for their clinical years.

We have identified 300 words which the student should be able to define. These are the subject of a series of multiple choice questions in which each foil has a feed back comment as to why the answer is the best or less good than another. By using these words as foils or correct answers it is easy to confirm understanding of the difference between look alikes such as a-, ana-, hypo-, or hyper-plasia without appearing to ask the same question twice. This series of questions is available with feedback for half of the first semester. Later the feedback is withdrawn and students are required to take a test comprising 100 random definitions from this list and to achieve 95% correct. They may take the test as often as they wish or need.

B) Concepts of disease process.

This is conventionally known as general Pathology. They can be conceived of as a series of flow charts which, when drawn out, appear insultingly simple. Thus the natural history of all neoplasms can be charted as follows.

Initiation - promotion - dysplasia - invasion - vascular transgression - metastasis.

Obviously large amounts of information are available about each step but fundamentally this and 8 other charts constitute the stuff of a semesters teaching. When stated, the flow is obvious, when placed as a foil in a multiple choice exam it is easily recognized and yet when students are asked to derive this they found it difficult. Computer teaching in this area is superb. The student is asked to select a word from the vocabulary list which is felt to be the first step, in say, an inflammatory reaction. In the authors

opinion this is tissue injury. Once selected, a few questions are asked about this before it can be set in place. Depending on the motif one can construct a daisy chain out of flowers, each wrong answer making the flower wilt and each correct one makes it grow until it fits the appointed place. A more macho image is the welding of links into a chain, when each wrong answer cools the link so it becomes less maleable. Whichever is chosen, the important feature of this game is that the student is forced to conceive his own flow charts rather than merely recognizing someone elses. At the same time factual information can be tested.

Identical data base and programming can be used to teach or test the student.

C) Specific organ system pathology.

It is here that the computer has least to offer. At the end of the course the student should be able to list large numbers of diseases and know some five or six facts on each. Books act as a magnificent repository of such information and little purpose is to be achieved by turning the computer into a page turner.

D) Disease morphology.

There is considerable controversy as to how much morphologic information a clinician requires. Should an average internist know that renal tubular carcinomas are yellow, or that Ewings tumor cells contain glycogen. (The answer must be no!) But if we accept that some macroscopic and microscopic morphology is a good idea then how best to teach it. Black and white illustrations or diagrams in textbooks serve as reminders to cognoscenti but do not assist the novice. Color atlases are beautiful but notoriously dull. Microscopy time is staggeringly consumptive of patience as well as student and faculty time. Prior to the videodisc the computer did not offer any assistance in teaching morphology. Now videodisc technology enables one to store 50,000 image frames or 30 minutes of movie or various combinations on one side of a disc. Linking the disc player to a computer is relatively straight forward and this enables one to use the computer as a guide to the Prado-like museum of visual images on the disc. The computer generates text, questions, answers and accesses the required image from the disc.

Thus we have a program on carcinoma of the cervix which starts by teaching relevant anatomy on diagrams which are computer generated. It then deals with exfoliative cytology by showing different smears and asking for a diagnosis. If the wrong answer is given the computer responds by telling the student that the answer is wrong followed by a display of what that wrong answer really looks like. Thus the individual who thought that a normal menstrual smear was trichomonas infection will be shown what trichomonas looks like and then returned to the original question for another attempt. Short movie sequences can be inserted when movement is important such as demonstrating techniques of surgery or scanning a microscope slide on low power. Once equipped with this information the student then goes to manage some simulated patients.

In summary, the two machines together can duplicate very closely the behavior of faculty in microscopy laboratories, with the advantage that many students are more comfortable with an inanimate, non-judgemental tutor. The same disc can be used as a resource for very different programs, thus cytotechnologists, medical students and gynecologic oncologists may be taken on very different pathways through the same material. Examinations can be conducted with very similar procedures.

Such a mechanism helps to teach concepts to non-microscopists. Teaching professional miscroscopists requires a slightly different technique. The most difficult step in microscopy is to select at low power that portion of the slide that is worth examining at high power. This can be done on videodisc but requires considerable skill. Thus a movie sequence of a low power scan of a blood film can be shown. The student is invited to stop the scan at any point he believes high power microscopy would be useful. When this instruction is given, the computer switches to a high power sequence after which various questions can be asked. This of course requires a more or less complete library of views at high power but with imagination one could accomodate most responses. Thus an instruction to view a totally uninteresting part of the slide at high power could trigger a question as to what the student was hoping to find. If the diagnostic area of the slide is not selected in say 5 attempts the computer then switches to a demonstration mode which states where inspection would be useful and why. Some six movie sequences of different diseases together with many still images can cover a wide range of diagnoses if used with imagination.

E) Use of laboratory tests.

This is probably best taught using clinical histories and asking the student to order various investigations. The results can be displayed and if one wishes normal values and costs can also be shown. Linking such a series to a videodisc to display radiology can generate a challenging clinical pathologic exercise. Most programs allow one answer to a given test but it is more realistic to allow variations, thus one in twenty results of any "normal" test can be programmed to show an answer outside the conventional range. Conversely, a request for steroid levels in a patient with Cushings syndrome can be returned as within "normal" range unless time of day is stated and repeated levels are requested. These nuances can be included in or excluded from the program depending on the type and seniority of the student taking the lesson.

Preparation, programming, and testing time is incredibly long for ones first attempt. One hundred fifty to two hundred hours per teaching hour is probably a conservative estimate. With practice of course this can be reduced but this method of teaching is never as quick as preparing a lecture or even writing a syllabus and probably always at least 10 times as long.

This brief review of the readily possible needs to be modified as to whether these activities are feasible and/or desirable. Undoubtedly lessons prepared on computer are vastly more consumptive of time than the traditional lecture. The preparer becomes significantly more knowledgeable about his

subject as a result at the price of considerable frustration. The audience gets a personal tour through data that is well worked but probably limited in scope with some problem as to how to get more information if needed. This potential improvement in quality is probably not worth the increase in preparation time unless the audience requires many exposures to the material or the audience is very large. Medical school teaching is one of the few surviving cottage industries and probably likely to stay that way in the foreseeable future. Audiences for teaching programs are likely to remain small, and if so, it would be cheaper to give the bulk of the course twice in the conventional way than to mechanise it. There are some exceptions to this general rule. Teaching vocabulary requires repetition beyond the patience of most faculty. If microscopic morphology is important, then microscopy labs are poor places to teach it because of the long apprenticeship required to master the instrument. Videodisc computer links make for a more efficient mechanism in this area. Case simulations for teaching the use of clinical lab tests have proved popular and instructive. In other areas, it is doubtful if computer teaching has sufficiently overwhelming advantages in quality to overcome the inherent problems of large start up costs.

TEACHING PROBLEM SOLVING IN PHYSIOLOGY WITH CBE

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Teaching Goals

In teaching physiology we want to help our students: 1) to understand the behavior of physiological systems on all organizational levels - from the molecular to the organismal and 2) to gain facility in solving qualitative and quantitative problems that deal with physiological systems on each of these organizational levels.

As with other skills, students need practice to become proficient problem solvers. Traditionally they have gotten this experience in small group activities like tutorials and laboratories. However, today we may supplement these other activities with computer based educational (CBE) exercises. This use is illustrated with examples from four of our exercises. All of the figures used here are screen prints from these CBE exercises.

Problem Solving With CBE

Our lesson CIRCSYS uses the simplified model shown in figure 1 to explore the pressure/flow/resistance relationships in the circulation.

Earlier in this lesson our "subject" had an arrested heart and no reflexes. He had been passively tilted into an erect position and the student was asked about the qualitative effect of

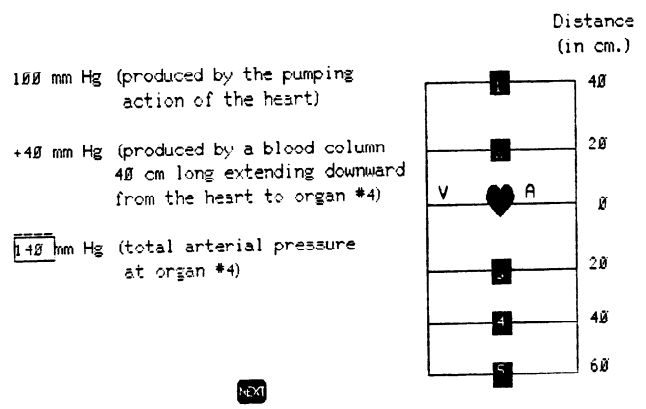
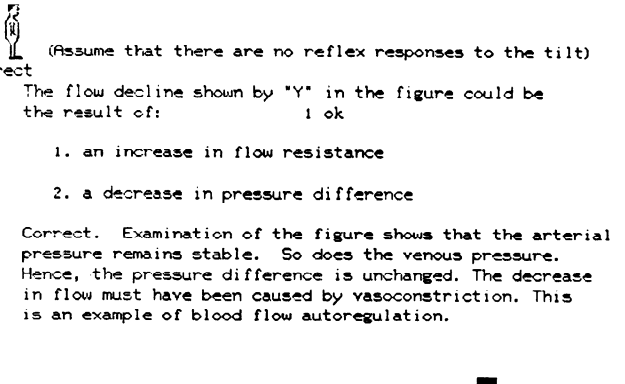


Figure 1. From CIRCSYS. The "subject" has been tilted erect and student asked to calculate the arterial pressure at organ #4. This was the student's second wrong answer so the method of calculation has been given.



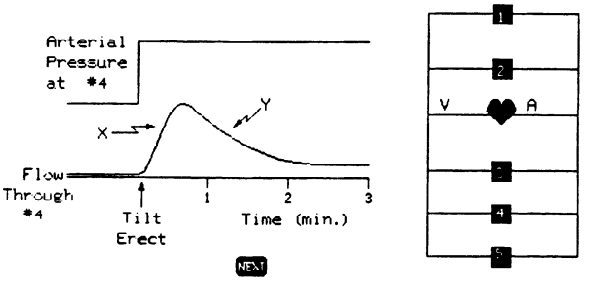


Figure 2. From CIRCSYS. The "subject" has again been tilted erect causing the pressure at artery #4 and flow through organ #4 to change as shown. The student has been asked to account for the flow decline at "Y".

this on the pressure in a lower part of the subject's CV system. This established that there is a static pressure in this fluid-filled system which increases from above downward. Now, as shown in figure 1, the student has to deal again with the same stimulus but this time applied after the subject's heart has been started. The distance of each organ from the heart is given in the figure and the student is asked to calculate the value of the arterial pressure at organ #4. The student is now expected to quantitatively apply the static pressure relationship.

Still later in the exercise (figure 2) the subject is again tilted erect and the local vascular control mechanisms that are activated by the now will known static pressure rise at organ #4 are explored.

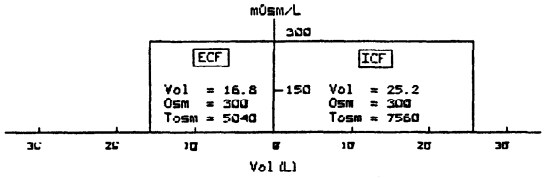
These three problems deal with the same relationship and together challenge the student to think about some of the complexity involved in a seemingly simple situation.

A second example illustrates how we expect our students to be able to determine the effects of perturbations to simple systems. This is taken from our lesson FLUID COMPARTMENTS.

First the student's knowledge regarding the distribution of fluid and solutes and the osmotic concentration of the body fluids of a normal subject is interactively examined. Then a Darrow-Yannet representation of the subject's body fluids is constructed (top of figure 3).

Following this the subject is given a large volume of water to drink, and the student is asked to evaluate the immediate consequences of this on the volume and concentration of body fluids and the way that this would affect the fluid distribution. The final outcome before the water load is excreted is then interactively determined.

We can represent the control situation with a Darrow-Yannet diagram.



Q11: What is the immediate consequence of absorption of 4 liters of distilled water from the gut? (There may be more than one answer)

A. Expansion of the ECF.
B. Expansion of the ICF.
C. Reduction of ECF osmolarity.
D. Increase of ECF osmolarity.
E. Reduction of ICF osmolarity.
F. Increase of ICF osmolarity.

Figure 3. From FLUID COMPARTMENTS. The student has calculated the values that have been used to construct the Darrow-Yannet diagram; and now has been asked to state the immediate effect of drinking a large volume of water.

Using this example as a model, a paradigm is developed for determining the effects of fluid gains or losses (figure 4). The student is then given another problem to work out. If the student has learned the method he should be able to determine the quantitative effect of almost any perturbation to the system.

Traditional physiology courses use the student laboratory as a problem solving experience. Computer simulated laboratory experiments may be used in the same way (1). However, a computer-simulated laboratory may be written to insure that the student is an active learner while the exercise is being carried out. For example, if the student is to do "an experiment", one can determine that s/he understands what the apparatus is, how it works and what kind of stimulus is to be delivered to the physiological preparation.

We can summarize the steps used to calculate the changes that occured in this subject.

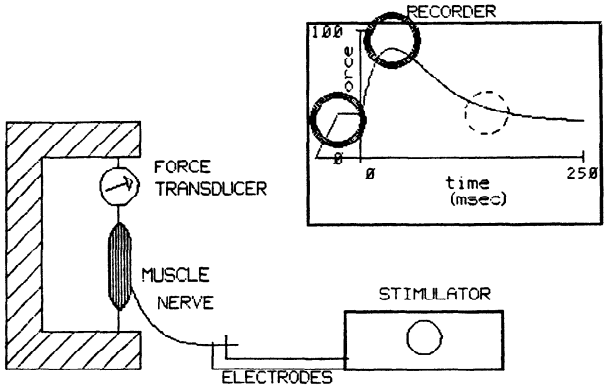
	TBW			ECF			ICF		
	V	Osm	Tosm	V	Osm	Tosm	V	Osm	Tosm
INITIAL	42.0	300	12,600	16.8	300	5040	25.2	300	7560
DRINKING 4L DH_2O	→			+4.0		+0			
RESULTS IN	46.0 →	274	← 12,600						
				→	274		→	274	
EQUILIBRIUM	46.0	274	12,600	18.6	274	5040	27.5	274	7560

The recipe for calcuating changes in body fluid compartments is thus:

1. Determine the new TBW (how much water was lost or gained?)
2. Determine the new total body solute (how much was gained or lost?)
3. Calculate the new osmolarity.
4. Given the total solute in each compartment and the new osmolarity calculate the new compartment size.

Figure 4. From FLUID COMPARTMENTS. The steps involved in calculating the values for figure 4 are shown graphically, above; and a general schema for the solution of such fluid-electrolyte problems is given below.

This is done in the first part of my next example a simulated student laboratory experiment called LENTEN, which deals with the length-tension relationship of skeletal muscle. Next the student is asked to demonstrate that he understands the source, form and information content of the physiological response by identifying the points on the recording that contain the information needed to construct the L/T curve (figure 5).



Now let's focus our attention to the "force vs time" record. What two data points on the graph do we need to save in order to determine the length-tension(force) relationship?

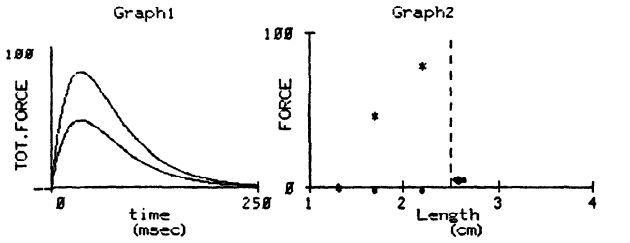
Right, we need to know the level of passive tension at each muscle length.

Yes, we need to know the maximum total force developed at each muscle length.

Figure 5. From LENTEN, a simulated student laboratory on the length-tension (L/T) relationship in skeletal muscle. Previously the apparatus was reviewed, the muscle was stretched and then stimulated and the passive elastic and contractile processes were reviewed. Now the student is identifying the data points to be used in constructing the L/T diagram. This figure shows the student's incorrect (dotted circle on the recorded twitch) and correct (thick circles) choices.

Then the experiment begins. The student is asked to stimulate the muscle at 7 additional initial lengths spanning a specific range. He does this by setting a length and then activating the muscle with the stimulator. The passive and peak tensions are automatically plotted in graph 2 (figure 6). However, rather than simply allowing the student to proceed in "cookbook" style, after the third trial the process is interrupted. The student must predict the approximate values of the passive tension and the maximum total tension after he has selected the fourth muscle length but before seeing the response (figure 6). The student's prediction is then compared with the result of the simulation. This prediction/comparison process is repeated until two consecutive correct predictions are made.

After enough pairs of data points are collected, the length/active tension curve is obtained by subtracting the passive tension curve from the total tension curve.



Initial Length	Passive Force	(Max.) Total Force
1. 2.2	0	78.25
2. 1.7	0	46.27
3. 1.3	0	0
4. 2.5		
5.		
6.		
7.		
8.		

Notice the dashed line and arrow on Graph2 at the length you've entered. To move the arrow up press [w] and to move the arrow down press [x]. Press [DATA] when you want to enter that arrow position as your prediction.

First, try to predict the passive tension that will be present. Your prediction of passive tension will be marked with a (x). Then at the same length predict the maximum force, which will be marked with a (o).

Figure 6. From LENTEN. The student has collected passive and peak tensions (graph 2) from three twitches (graph 1) at the initial lengths shown in the table. A fourth initial length has been selected but the student must predict the values of the passive and peak tensions before the muscle can be stretched and stimulated.

This interactive exchange at the computer terminal not only simulates a physiological experiment, it simulates what a good teacher does in the laboratory. He pokes, prods, questions and otherwise tries to keep his students actively observing the experiment. He keeps them thinking about what they are doing while they are doing it and about what they are seeing, while it is happening. He challenges them to consider what it all means.

The hardest thing that our students have to learn is how the pieces of a system are integrated into a functional unit. We have noticed that even our better students often don't know how to use the information that they have learned. Although many students can explain responses after they have seen them, they cannot predict what will happen in advance. We therefore think it is important to give them experience with this kind of problem solving activity.

This is illustrated in the last example, HEARTSIM (2). The cardiovascular simulation in this exercise is the well-known MacMan written by Dickenson and his co-workers (3). However, the "heart" of HEARTSIM is the predictions table, illustrated in figure 7. When the student does the first procedure he is instructed on the completion and use of the table. In this example the student's problem is to predict the qualitative effects of reducing arterial resistance to 1/2 of its normal value.

In the first column the student has predicted the direct response to this stimulus (DR, the immediate physical consequences). These are the changes that one would see in an individual without reflexes and are the main source of the initial component of transient behavior.

The first time the students do the exercise the eight parameters in the table are presented one at a time and the student receives feedback after making a DR prediction about each of them. In the process, certain cardiovascular relationships are identified (figure 7 under the Predictions Table) and the student is cautioned that his predictions must agree with these.

After the student has completed the first column he makes two more sets of predictions. He enters the effects of the baroreceptor reflexes in the second column (RR) and the changes from control that will be present at steady state into the third column (SS). No feedback is provided about these predictions at this time.

When the table has been completed a two stage review of the student's input takes place. First, the three predictions for each variable are reviewed. These must be logically consistent, i.e. DR and RR must sum to produce the SS response. Next the predictions are checked to see that they do not violate any of the identified CV relationships. In the example shown in figure 7 there is one such error. This is pointed out to the student who is given a brief explanation.

Once this review is finished, the simulation is run. The student sees a plot of blood pressure and heart rate as a function of time and a table of the initial and final values of the computed variables. Then the simulation results (both quantitative and qualitative) are then entered into the predictions table (figure 8). Disagreements between these and the student's predictions are highlighted and are then individually discussed with the student.

PREDICTIONS TABLE

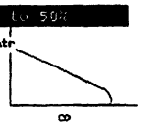
Parameters:	DR	RR	SS
Heart Rate	0	↑	↑
Stroke Vol.	0	↑	↑
Cardiac Out.	0	↑	↑
Card. Contr.	0	↑	↑
Art. Resist.	↓	↑	↑
Mean B.P.	↓	↑	↑
Atrial P.	0	↑	↑
Capillary P.	↑	↑	↑

relationships: $CO = HR \times SV$ $BP \sim CO \times R_a$
$P_{atr} \propto 1/CO$ when CO is an independent variable

PROBLEM 2 a

Arterial Resistance is decreased to 50%

As an independent variable, increased cardiac output decreases atrial blood volume and therefore it lowers the atrial pressure. This relationship is shown in the graph. Your predictions do not agree with it. Please correct your predictions.



Press [SHIFT][NEXT] when you have finished making corrections.

Figure 7. From HEARTSIM. In this tutorial-simulation of the cardiovascular system the student must predict the effects of each stimulus before he is shown the simulation (reference 3). The student has done this but has violated one of the previously identified relationships (shown under the table). In this figure the program is reacting to the error.

PREDICTIONS TABLE

Parameters:	DR	RR	SS	Control	Steady State
Heart Rate	Ø Ø	↑ ↑	↑ ↑	72.9	138.2
Stroke Vol.	Ø Ø	↑ ↓	↑ ↓	67.9	45.Ø
Cardiac Out.	Ø Ø	↑ ↑	↑ ↑	4.9	6.2
Card. Contr.	Ø Ø	↑ ↑	↑ ↑	1.3	2.1
Art. Resist.	↓ ↓	↑ ↑	↑ ↓	16.Ø	9.6
Mean B.P.	↓ ↓	↑ ↑	↑ ↓	9Ø.3	71.5
Atrial P.	Ø Ø	↓ ↓	↓ ↓	1.8	Ø.9
Capillary P.	↑ ↑	↑ ↑	↑ ↑	12.7	14.6

The left sign in each box is your prediction.
The right sign is the Heartsim prediction.

4 of your predictions don't agree with the simulation.
Press SHIFT NEXT for a review of some of these errors.

Figure 8. From HEARTSIM. The simulation has been carried out and the output entered next to the student's predictions. Differences are shown and will be discussed.

At the time that our students do HEARTSIM they have heard our lectures, read the textbook and studied our syllabi. However, none of these media seem to enable them to fully understand the complex, dynamic behavior of the CV system as a whole. Nor do they challenge them in a way that helps them to easily solve problems involving stimuli to the system. Those traditional experiences alone do not teach them to " think in physiology". However, HEARTSIM and other CBE exercises do help them achieve this goal.

Benefits of CBE

What, then, are the benefits of CBE exercises. As these examples show, computer programs may be written to illustrate, demonstrate and simulate relationships, system states, system behavior and student experiments. However, if students merely sat at a terminal and were fed material by a computer we would only have created a one-on-one lecture hall using a very expensive visual aid. A well designed CBE exercise will continuously involve students in an intellectually challenging way. They will not be permitted to simply be passive recipients of information. Instead they will have to be constantly thinking and observing to provide the input that is required to keep the CBE program moving.

A second, very important feature of this process is that it provides students with feedback for every entry they make. This reduces the chance that they will misunderstand the material that is being reviewed. It helps them to correct errors in their problem solving efforts immediately after they make those mistakes. It also reinforces correct inputs and helps students who already are doing well to do still better.

A student who correctly answers a question does not get the same feedback as one who is wrong. In fact each of these students experiences a quite different sequence of interactions. In other words, the CBE experience is individualized to match each student's knowledge and problem-solving skill. Thus one avoids the problem that arises in small group discussions when there are students with widely different levels of preparation or ability simultaneously vying for the help of one teacher.

Yet another benefit of CBE is that it may be used ad lib. Students may do an exercise when they are prepared, not when it appears in an inflexible schedule. Nor do they have to finish it in one sitting. Properly designed courseware will allow them to stop part way through and resume later where they left off. Also students may do an exercise more than once if they choose.

Another feature of CBE courseware is that it may be designed and written by the best, most experienced teachers available. Thus over the lifetime of the exercises, every student who uses them has the benefit of learning from a teacher with superior ability. One cannot hope to duplicate this in the lecture hall, laboratory or tutorial classroom because the best teacher will not always be available.

Finally, CBE exercises can be fun to do. We find our students getting involved with the "patients" in HEARTSIM. One hears that "he" or "she" did this or that as students anthropomorphise the program in the computer terminal.

Conclusion

In conclusion, CBE is beginning to provide our students with a new kind of learning experience. This medium has characteristics that usefully supplement the more traditional physiology teaching techniques. It is especially beneficial in providing our students with much needed problem-solving experiences in challenging but flexible and personally tailored ways. Our hope is that this process will help our students to improve their ability to solve real world problems with their physiological knowledge.

We are deeply indebted to our Office of Computer Based Education for the advice and service that they provide us.

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USING COMPUTER MODELS TO UNDERSTAND COMPLEX SYSTEMS

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ABSTRACT: Teaching and research in physiology encompass increasingly complex notions of the system under study. Computer modeling fosters understanding by extending one's ability to formulate, test, and evaluate one's hypotheses about the system, and to describe expermental data. The exploration of the model system's behavior serves teaching and investigation in analogous ways.

As physiological investigation and insight penetrate to deeper and deeper levels inside the biological system, the degree of known or recognized complexity increases. The complexity is real, because the cells, organs, and organisms are endowed with multiply-redundant feedback-control systems which enhance the reliability of the overall system. Because of the complexity, artificial aids to one s intuition become more and more important to gaining a thorough understanding of the system. Mathematical modeling is such an aid.

The process of modeling begins with data acquisition and verbal description. The physiological system can usually be represented so as to raise the question of causality, which in turn provides the development of an hypothesis. A fully expressed hypothesis normally provides predictions as well as explanations, and thereby leads to defining successively more stringent tests of the hypothesized causal relationships.

THE MODEL AS A HYPOTHESIS: The modeling process is therefore merely the formulation of a hypothesis from which predictions are made and compared with real-world behavior. A model, however, is simpler than the real thing. Like any simplification, it provides only a parsimonious and somewhat erroneous description. The overall objective of the process is to maintain the minimal level of complexity that provides the desired minimization of error. To reduce the difference between model and physiological observation ordinarily requires making the model more complex. One must overcome the barriers to abandoning simplicity to attain increased realism. Because in biological modeling it is the approach to realism (evaluation with experimental data) that brings insight into the unknown aspects of the system, the sacrifice of the easily-learned simplicities becomes an unavoidable feature of the quest for reality. In each phase of its development, the model should be compared with reality; a model can be regarded as valid only to the extent that it corresponds to reality.

The design of a model inevitably involves a compromise between an attempt to describe the whole complexity of the real system and one's ability or willingness to deal with this complexity. In chosing a usable design one tends to define a model within a given hierarchical level. The distinction between heirarchical levels is somewhat arbitrary, but one tends to think of a set of operations describable in similar terms (e.g., flows, volumes, conductances) as being on one level, and of mechanistic details being on a more basic physiochemical level (e.g., blood rheology, membrane transport, molecular diffusion).

Modeling is an attempt to put into overt form one's knowledge about a system. Inevitably, this means expressing a particular viewpoint influenced by prior experience and knowledge of detailed aspects of the topic under study. The usual goal is to formulate a comprehensive, integrated, and quantitative expression of one's working hypothesis on the nature of the system. A working hypothesis may be one of a few alternative hypotheses that are to be tested by experimentation, or may simply serve as the summarizing view of the testing that has been done thus far. In either case the model, the synthetic analog to the system, can also serve as the vehicle for designing the next tests of the system which are always needed in order to refine one's understanding of the system.

If putting all of one's information together in a comprehensive package is too expensive in terms of time, effort, or whatever, then the model will necessarily be focused on a particular objective, and contain some biases with respect to a particular point of view. Computers, now having large memories, and running at high speed, restrict the process much less than formerly, and, in fact, invite the formulation of more complex models than have previously been sensible to undertake. The supercomputer revolution is now beginning to open up new vistas by virtue of offering large memory and high computational speed so that highly realistic, even though highly complex, models can be formulated and run in a practical manner.

The modern investigator using modeling tools can enjoy the luxury of developing an acceptable all-encompassing view of the system, trying to figure out its real structure and behavior without being bounded by the limitations of one's personal ability to calculate or to develop analytical solutions. Analytic solutions for complex systems are often not available, and even when they are, they may not be computable; some complex "analytical" solutions can only be transformed into digital representation by an immense amount of computation, and even then may lack accuracy. While one would certainly not like to be caught advocating inaccuracy, situations abound in which it is more practical to use numerical solutions not only for speed, but also because they can provide 2 or 3 digit accuracy while the so-called analytical solution may prove quite unmanageable. It is much better to develop a relatively good model with 3 decimal digit accuracy than to develop a simpler, unrealistic model with 6 digit accuracy.

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MODEL FORMULATION: The process of formulating a realistic model requires much sorting and sifting of the available information. The evaluation of the published or unpublished literature and of one's own observations is an inevitable source of bias; while the bias cannot be fully overcome, it tends to be minimized by additional requirements useful to superimpose to ensure realism: conservation of mass, charge, volume, and the linear progression of time. The modeler can use these overtly, going beyond checking the units to quantitate formally the physical attributes of the elements. The general principles have been very nicely described by Berman (1963).

Any modeling requires making assumptions, each of which should be justified carefully. Making the assumptions explicit is a first step, forcing examination of the reality of each element of the hypothesis. Is each assumption *quantitatively* valid in the proposed setting?

Sometimes a hypothesis can be so well-formulated that explicitly stated or reasoned parameter values can be used without adjustment as components of the hypothesis, giving rise to predicted results which matches observed experimental results. Such a success does not prove the hypothesis correct, but supports the underlying notions of causality and provides a framework upon which the design for other experiments can be explored.

Simplification of the model by reducing its complexity is an important goal. But there are risks in succumbing to the natural tendency to use the most simple model. The question of acceptability in the simplicity is a quantitative one that can usually be evaluated. One mechanism for evaluating simplified assumptions is to build a comprehensive model that is sufficiently complex and realistic to describe a wide variety of relevant experiments, and then to test the simpler models against it. In specific cases, albeit rather limited ones, compartmental models (linear lumped models or mixing pool models) can give adequate representation of spatially distributed blood-tissue exchange regions. For example, when the capillary barrier permeability is extremely low then the representation of the interstitial fluid region as a first order mixing chamber is not bad. On the other hand, when the conductances for fluxes into specified physiologically defined regions are moderate or high, then the compartmental representation fails, and axially-distributed systems, often with concentration-dependent conductances, need to be considered.

An example of modeling in our laboratory concerns blood-tissue exchange in cardiac and skeletal muscle (Bassingthwaighte and Goresky, 1984). It is the basis of our experiment design and our analysis. The elementary processes to be described are the local flows, permeation of the capillary membrane, distribution throughout the interstitium, permeation of the sarcolemmal membrane, and consumption inside the cells. One begins with the anatomy, incorporating estimates of volumes of the capillaries, the distances between them, their surface area, and equivalent information on myocyte surface area and volume. The modeling must account simultaneously for intravascular, interstitial, and intracellular events. Within the organ intravascular substances are dispersed by velocity gradients radially in large vessels, by molecular diffusion, by eddy currents, and by heterogeneities of flows and vessel lengths. A gross overall description of the total effect of all of these is provided by observing the transport across the organ for a substance which remains within the blood stream; albumin and larger molecules can serve as indicators for this purpose.

For substances which enter the interstitial space, the rates of axial and radial diffusion, and of binding to ground substances need to be determined. A feature of the exchange processes in muscle is that diffusion parallel to the capillary is slow compared the convective movement or to permeation of the membranes. The result is that there are concentration gradients along the capillary-tissue units; accounting for these in the modeling can be done, but only at the expense of representing the gradients explicitly, which is usually accomplished by approximating each continuous region by a sequence of subregions of differing concentration. Since characterizing the transport of an extracellular substance is a prerequisite to understanding the transport of a metabolized substrate, refined experiments will make use of sucrose or cobaltic-EDTA (Bridge et al., 1982) as the reference solute. Actually, the ideal extracellular reference is one of the same molecular weight and hydrophilicity, lipophilicity, etc., as the substrate of interest.....L-glucose is the ideal mate for estimating the cellular uptake of D-glucose.

Radial diffusion needs also to be considered. If the resistances imposed by diffusion across the capillary or interstitium or inside the cell approach the resistance imposed by the cell membranes or the capillary wall, then these must also be accounted for in the modeling . Fortunately for the modeler, and presumably for the efficient delivery of substrate to cells, extracellular diffusion distances are so small in normal tissues and the process is so fast that an assumption of instantaneous radial diffusion is quite reasonable.

Features of the system at the next more basic heirarchical level are the transport processes themselves. When using tracers in the presence of constant concentrations of non-tracer mother substance, linear conductances can be used to describe membrane conductances, but when concentrations change in spatial location, or in time, then concentration-dependency of the transport rates (as in Michaelis-Menten kinetics) must be accounted for.

MODELS IN EXPERIMENT DESIGN: The use of the model in experiment design is an example of how modeling can expand and extend one's creativity. The mere process of testing the model to see "what happens if..." tests the model, the modeler's thinking, and, if the proposed experiments appear reasonable, define a specific hypothesis which is to be tested by experiment. This "mind extending" feature of the modeling makes experimentation more efficient. The ability to answer the "what if.." within the context of each of several models with similar purposes provides the possibility to distinguish between models, some necessarily having behavior closer to that of the real system than others.

The blood-tissue exchange models are used, for example, to help define experiments to measure the rate of entry of D-glucose into myocytes within an intact heart. By testing model solutions it was quickly learned that having an intravascular reference tracer was critically important; in effect, using a substance whose dispersion and delay was completely explicable in terms of intravascular events was the key step in developing a method for estimating transport rates across the membranes, as proposed by Crone (1963). It was also the basis of the concept proposed by Chinard et

al. (1955) for estimating extravascular volumes of distribution. This advance allowed the estimation of capillary permeabilities. However, "thought experiments" done on the model, looking at solutions with noise added in accord with expectations from laboratory experience, indicated that the next stage of analysis required something more. The problem was that estimates of cellular uptake and intracellular volume of distribution showed significant inaccuracy in situations where the rate of uptake was not high.

The solution was in finding an indicator that remained extracellular but otherwise behaved like D-glucose; L-glucose was the ideal candidate. The differences between the time course of exchange for L-glucose and that for D-glucose are fairly subtle, as might be expected since the A-V extraction of D-glucose is only a few percent. When "thought experiments" were done on one, then the other, with small fluctuations allowed in flow and in noise in the model solutions, the differences were too small and too variable to interpret in terms of cell permeability. Consequently the only way to make accurate comparisons between the two for the purposes of estimating permeation and consumption rates is to record data on the two substances simultaneously, so that the same biologic fluctuations and experimental noise affect both, and apart from isotope counting statistics, affect both in the same way. The argument extends a step further by the same logic, namely that one must also record data from the intravascular indicator simultaneously in order to identify the capillary permeability and interstitial dilution volume for the extracellular substance. Thus the experiment of choice is to make brief injections, a pulse of a second or less duration, so that the entering waveform has the highest possible sharpness, for 3 indicators simultaneously, while recording the concentration-time curves for each of the three in the venous outflow or from specific regions within the organ.

MODELING ANALYSIS: Analysis via modeling implies the fitting of models to the observed data. This is a tedious process requiring adjustment of the values of parameters of the model, in a meaningful fashion, until a close fit is obtained. There are a number of general purpose computer programs available in the public domain for doing this, but we have found that more efficient techniques can be developed for specific purposes. Some of these have turned out to be of general value for a wide range of functions (e.g., Levin, Kuikka, and Bassingthwaighte, 1980).

Noise in the data affects parameter estimation. An evaluation of the effects of noise may be provided via computer routines which optimize the fit of the models to the data and provide estimates of confidence limits based on theory of least squares. An alternative brute force approach is to produce a model solution with known parameters, to add noise to the idealized "data" obtained in the form of model solutions, and to fit these "data" with the model using automated optimization routines to obtain estimates of the parameter values. On repeating this operation many times, a distribution of the estimates of the parameters can be obtained for each level of noise. These distributions of estimates can be compared with the true value and assessed from the point of view of whether the distribution of estimates is distributed randomly or in some skewed fashion, which is usually the case. Least squares approaches tend to underestimate the error and cannot show skewness.

Good modeling analysis is based on fundamental principles of conservation and of self-consistency of the concepts involved. Examination of the models by qualitatively different experimental approaches is essential to their testing; ultimately each model will prove to be incorrect or incomplete, leading to new hypotheses which are then to be tested by yet more refined experiments. Techniques and approaches which are sufficiently general and well-defined are usually applicable to a wide variety of situations, not simply one experiment. This makes the modeling a worthwhile investment.

MODELING TECHNOLOGY FOR DESIGN AND ANALYSIS: Interactive modeling is the most facile route to design and analysis. Nowadays there are a number of commercially available packages for modeling which include graphical display of the results while the solutions are being computed. Some of these adhere to a committee standard for a Continuous System Simulation Language (CSSL), while others provide for an interface to a model constructed in Fortran or Basic. Our SIMCON (for SIMulation CONtrol) is merely an interface which allows great flexibility in parameter control, display, and interactive adjustment (Anderson et al., 1970). One of its useful features is permitting automated stepwise adjustment of a parameter whose influence is being explored. Another is the ability to interrupt solutions any time, when the waveform is predictable or undesirable. A good practical system for performing compartmental analysis is provided by SAAM, originally developed by Berman (Foster and Boston, 1984).

Current systems allow not only model formulation and manipulation but also the display of data and optimization, the automated adjustment of parameters to produce a solution fitting a chosen set of data. Future systems are being designed to allow model formulation without programming in a computer code language by using ikons representing differential operators or other mathematical operations to represent functions; the modeler chooses the arrangement of ikons that best represents his hypothesized system. Before this approach can have great power it is necessary to develop a good many operators which are more applicable to biological systems than are the standard operators of electrical networks, handy though these may be. Examples include operators to describe capillary-tissue units, as described above, or neuronal cables, or other moderately detailed functions which are components of systems.

MODELING AS A TEACHING TOOL: Many features of the modeling process lend themselves to the teaching situation. Whether modeling be considered as a particular aspect of artificial intelligence, or a variant on the Socratic approach, or merely a form of "assisted analysis," both the development and the use of detailed models of complex systems foster understanding. The modern use of the computer is as an extension of the mind, using it to predict system behaviour from the underlying principles and from previously observed events. While the computer displays and simulations should not and can not substitute for observations of nature, they can assist by alerting the student's mind to what might be expected, as well as alert the investigator as to what can be learned from a given experiment. What works for investigators should work for students, for what researcher is not a student is his own field, and what student is not an investigator at an earlier stage of development?

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COMPUTERIZATION OF THE STUDENT NEUROPHYSIOLOGY LABORATORY

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The purpose of this article is to describe how we have computerized a traditional Neurophysiology laboratory course. In the past students have always worked with analog data, accessed and displayed on a polygraph or an oscilloscope. With the advent of affordable digital computers, it is now possible for students to work with digitized on-line data.

Computerizing the Neurophysiology laboratory has numerous advantages including speed, accuracy and reliability in the acquisition, reduction and analysis of data. In addition, the digital computer performs unprecedented signal processing. It permits the student to analyze previously unmeasurable electrophysiological phenomena such as auditory cortical or brainstem evoked potentials. Additional advantages accruing from the computerization of student experiments are the ease of data analysis and the multiple formats for data display. To initiate the computerization of the student Neurophysiology laboratory we have created one prototype work station consisting of all the hardware required to perform 10 specified experiments.

The computer, presently dedicated to the student work station, is a Cromenco with two disk drives, the Z-80 chip and an S-100 bus. The computer is fitted with two analog-to-digital and digital-to-analog converters. One, a Cromenco 8-bit D+7A, is used only for setting the intensity of a stimulus or controlling some other peripheral; the other, a 12 bit, 16 channel A/DC, is used for data acquisition. The sampling programs are written in Assembler language and are designed to sample two channels of data at different rates. The terminal is an ADM-3A Lear Siegler, and the printer is an IDS-60 Paper Tiger.

Four generic computer programs, tailored to the particular requirements of each experiment are: 1) INSTRUMENTATION, 2) HAMMER, 3) STIMMU and 4) ACEP (i.e., auditory cortical evoked potentials) and BAEP (i.e., brainstem auditory evoked potentials). INSTRUMENTATION is used to introduce and instruct the student about the use of the major pieces of equipment used throughout the course. In addition to the computer, terminal and printer, the equipment includes a Hewlett Packard broadband oscillator, a Tektronics storage oscilloscope, an EMG amplifier, and power supplies for the transducers and stimulators which are computer interfaced. In Experiment #1 the student is guided through the use of each of these pieces of equipment with step-by-step instructions displayed on the terminal screen. In addition to the computer instructions the student is provided with a **Laboratory Manual** whose contents permit the student to test his comprehension of each experiment's physiological objectives by providing questions and pertinent references to the scientific literature. The highly motivated student may proceed to whatever depth of the topic he desires. An insecure student can repeat any part of the experiment until he masters the concepts being presented. The instructions in the manual and those presented by the computer are sufficiently detailed that a student should be able to work independently whether an instructor is available or not.

The computer program called HAMMER is used in experiments requiring a mechanical stimulus to evoke the response being studied. The phasic monosynaptic reflexes like the jaw jerk and the Achilles tendon reflex are examples. In both of these experiments mechanical stimuli, namely controllable taps, are required. We use a solenoid driven plunger as the mechanical stimulator. It is interfaced with the computer so that the current to the solenoid can be controlled by the student from the terminal's keyboard. A piezo-electric transducer is placed in series with the solenoid's plunger to provide a measure of the dynamic impact force of each tap. Tap forces and the evoked action potentials of the stretched muscle are digitized and stored in computer memory.

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The computer program called HAMMER provides the following menu for data handling:

1) Data acquisition: single trials
2) Data acquisition multiple trials
3) CRO display of data
4) TABLEs and statistics
5) SCATTERGRAMs
6) Curve fitting
7) exit

This program and the others provide students with tremendous flexibility for data analysis and data reduction. The student in a very short time can easily obtain sufficient data to make statistical analyses feasible and meaningful. The computer programs also provide choices of statistical tests and options for curve fitting. The students may see their data on the CRO or print it out as hard copy for their data books.

Another program, called STIMMU, is used in all experiments requiring electrical stimulation such as the analysis of the properties and propagation of action potentials in isolated peripheral nerves, the determination of the contractile and electrical properties of isolated skeletal muscle, the measurement of the conduction velocity of a human peripheral nerve, or the analysis of the H-response. The philosophy underlying both the HAMMER and STIMMU programs is similar, in that each provides the student with multiple options for data acquisition, storage and analysis.

Another computer program has two forms, ACEP.COM and BAEP.COM, permitting the student to study the Auditory Cortical Evoked Potentials and Brainstem Auditory Evoked Potentials. Prior to the advent of the microcomputer with its averaging capabilities neither of these experiments was feasible in the student laboratory.

Electromyograms and EEG are the only experiments which do not lend themselves to computerization in the student laboratory. The microcomputer's memory is too small to store enough digitized data to make a meaningful analyses. Therefore, students will perform these experiments in the traditional way, i.e., recording analog signals on a polygraph and analyzing records by hand measurements.

Evaluation of each experimental protocol is underway. Upon completion of an experiment, the volunteer students write an evaluation of the manual's instructions and of the computer programs. Then we revise the manual, the computer program, or both in accordance with the students' recommendations. Subsequently, other students perform the revised experiments and provide their consturctive criticisms. The course will be "up-and-going" for at least two groups of four students by September 1985. The two groups will use the same prototype work station, but on different days of the week.

We hope that this computerization of the student Neurophysiology laboratory will serve as a model for the computerization of student labs in other areas of Physiology.

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USE OF COMPUTER SIMULATIONS TO PROMOTE ACTIVE LEARNING IN MULTIPLE TEACHING SETTINGS

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Background

In 1975, Modell et al. (4) completed a series of simulations in respiratory physiology designed to provide "laboratory" exercises for students in an independent study setting. These programs provided tabular data consistent with variable values chosen by the students. A "laboratory" manual provided direction for using these programs.

Although these programs proved very helpful for students (1), their use in other teaching settings was limited by the tabular nature of the output, the absence of video monitors suitable for viewing 80 column numerical data by large groups, and the high cost of computer graphics.

The advent of microcomputers and the emergence of high quality video projectors have provided inexpensive graphics capabilities and a means by which to display the computer output on a large screen. These developments have made it feasible to consider incorporating simulations in large group presentations. In addition, the portability of the microcomputer makes it possible to use this vehicle in virtually any classroom.

We have recently completed revising the original set of simulations to include one or more graphical representations as part of the output of each program. The revised outputs are designed to provide a conceptual aid to understanding the physiology involved, an indication of where values are "measured", or a description of the model and how it is solved (5). The revision enhances the information conveyed by the programs such that they can become valuable aids in conference room and lecture hall settings.

Simulation Overview

The revised set of simulations includes 12 programs covering respiratory mechanics, gas exchange, chemoregulation of respiration, ventilation/perfusion relationships, and acid-base balance (Table 1). The philosophy underlying the revision is the same as that followed for the original programs (3). As in the original series, a "laboratory" manual accompanies the programs providing direction for students in an independent study or student laboratory setting. The revision was designed for the Apple II family of computers, although the set will also be adapted to IBM PC compatible computers.

TABLE 1. OVERVIEW OF REVISED RESPIRATORY PHYSIOLOGY PROGRAMS

Program Title	Material Covered
Static Relationships	Elastic properties of the lung, chest wall, and total respiratory system
Dynamic Relationships I	Effects of lung compliance and airway resistance on development of a tidal volume
Work of Breathing	Oxygen cost of elastic, resistive, and total work during inspiration
Dynamic Relationships II	Respiratory dynamics in terms of the total respiratory system (lung and chest wall)
Alveolar Gas Exchange	Gas exchange between the atmosphere and the alveolar compartment
Chemoregulation of Respiration	Oxygen and carbon dioxide response curves
O_2 and CO_2 Dissociation Curves	Interrelationships between the O_2 and CO_2 dissociation curves
Exchange from Atmosphere to Tissues	Influence of alveolar ventilation, cardiac output, and anatomic shunt flow on arterial blood composition and gas exchange at the tissues
Gas exchange in a Single Alveolus	Influence of ventilation-perfusion ratio and inspired gas on gas exchange in a single gas exchange unit
The Non-Uniform Lung	Gas exchange from atmosphere to tissues with a lung having high and low ventilation-perfusion ratio areas
Overall Gas Exchange	Gas exchange from atmosphere to tissues with a lung having high and low ventilation-perfusion ratio areas and an anatomic shunt
Acid-Base Balance: Fundamental Relationships	Acid-base balance from a Base Excess point of view

Program Example

The graphical portions of the output of the first program in the series are shown in Figures 1 and 2. This program allows the student to study the influence of changes in elastic properties of the lung, chest wall, or both on the characteristics of the total respiratory system. The student describes the subject by providing values for the resting (undistended) volumes of the lung and chest wall expressed as per cent of Total Lung Capacity (TLC), compliance of the lung and chest wall expressed as per cent of normal, and a pressure applied to the respiratory system to displace it from its resting volume. TLC is assumed to be 6 liters.

Figure 1 shows the first pictorial output provided in response to the student's description of the subject. The screen first reinforces the definition of resting volume as the volume at which the pressure difference between the inside and outside of the structure is zero. The lung and chest wall are each represented by a bellows proportional in size to the resting volumes chosen by the student.

Along with the numerical data, the graphic shows that the lung and chest wall interact to determine the properties of the respiratory system (double bellows, proportional to the resulting resting volume of the system). From this graphic, the student can see that, if the coupling between

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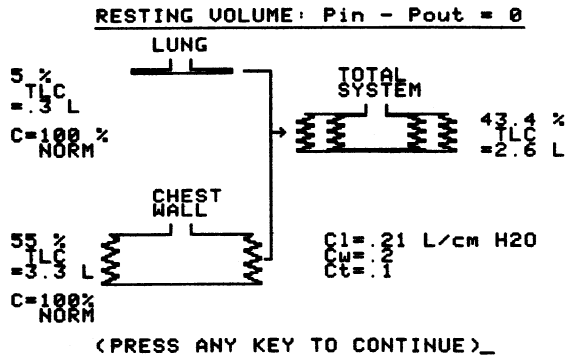

FIGURE 1. First pictorial output from 'Static Relationships' program. The student provides values for the resting volumes of the the lung and chest wall (% TLC) and compliance of the lung and chest wall (% normal). The model calculates the resting volume of the system (FRC) and the lung, chest wall, and total system compliance at FRC.

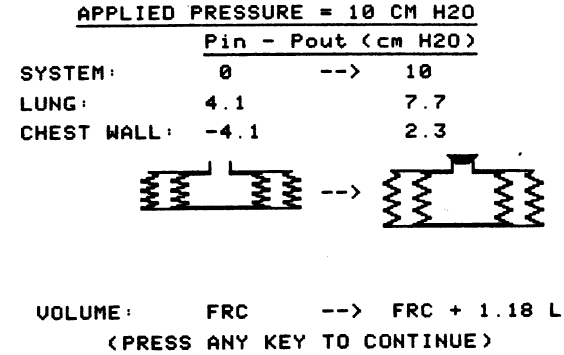

FIGURE 2. Second pictorial output from 'Static Relationships' program. The student has applied 10 cm H_2O pressure across the respiratory system. Pressures shown on the left are for the resting volume of the system (FRC) determined by the data shown in Figure 1 (muscles relaxed, airway open). The right side of the graphic shows similar data after pressure has been applied to the system (muscles relaxed, airway closed).

the lung and chest wall is removed (e.g., a pneumothorax), the lung will return to its resting volume, and the chest wall will return to its resting volume.

Figure 2 shows the second pictorial output for this program. The student has applied 10 cm H_2O pressure across the system. The output indicates that the system has gone from its resting volume (FRC) to 1.18 L above its resting volume. In addition, the output shows the student how pressures across the lung and chest wall contribute to the pressure difference across the system.

After these outputs have been presented, the data can be saved for future reference or compared to previous "experimental" runs.

Use in the Classroom

For the past 4 years, we have used 9 of the 12 programs in small group conferences (20 students) during the respiratory physiology portion of the medical school curriculum. Initially, we used multiple video monitors for displaying the output in this setting. However, because this proved to be less than optimal, we have used a 40-inch projection television for the past 2 years.

The programs are used in the conferences to review material presented in the conventional lecture portion of the course and to help answer questions that the students may raise during traditional problem solving sessions. When using the models, the students play an active role in determining input values. Before the model is run with a given set of chosen values, the students discuss the expected results and the rationale for predicting these results.

Student response to this format has been favorable, and a significant number of students request access to the simulations for independent study.

Use in the Lecture Hall

One program (Alveolar Gas Exchange) has been used in the lecture hall with the entire medical class (175 students). In this setting, the output was projected on the same screen as that used for slides with a video projector (2). After presenting a brief introduction in a standard "lecture" format, the model was used to discuss alveolar gas exchange in a "workshop" mode. In this mode, the instructor served as discussion leader, posing questions that could be answered by experimenting with the model. Again, members of the class chose input values, and the output was discussed before and after it was displayed.

Using this format, it was not difficult to involve a large portion of the class in the discussion. Thus, students who would usually be passive members of the "audience" became active participants in a discovery learning activity.

Conclusion

The microcomputer, coupled with large screen display, represents a potentially powerful tool for transforming the large group classroom encounter from an environment in which students act merely as "recorders" of information to one in which they become active participants in a discovery learning process. Judicious use of simulations, whether they be mathematical models or patient encounters, represent the key to this transformation.

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AN INTEGRATED CARDIOVASCULAR TEACHING LABORATORY

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Previously we have demonstrated a laboratory simulation on a microcomputer for studying the mechanical actions of the left heart. This project extends that work to emphasize teaching of an integrative view of cardiovascular physiology. Three components are employed: (1) a group of simulated laboratories which emphasize an explicit integration of ideas, (2) fault-finding exercises in which those ideas may be put to practical use, and (3) a testing device capable of measuring student progress, from inexperienced to expert understanding.

Introduction

A major goal in teaching physiology is to teach its integrative aspects. Unfortunately, there seems to be confusion among physiologists as to the meaning of integrative physiology. We like to make a distinction between two terms: integrated physiology and physiologic integrations. By integrated physiology we mean those processes working within the natural system to bring about coherent global behaviors of an organ system or organism; homeostasis and cyclic behavior are examples. By physiologic integrations we mean the mental constructs required to understand and work with an integrated physiologic system. The former is natural, the latter is artificial--a man-made construct that aids comprehension and problem solving.

Certainly it is important to teach both aspects of integrative physiology but in so doing it is important to understand the differences between them. When the stated goal is to foster in the minds of students a mental construct that allows synthesis of knowledge so as to facilitate its use in solving problems, the objective is clearly one of teaching physiologic integrations. To meet that objective, we have been developing three types of computer-based tools: simulated laboratories for explicit demonstration of integrations, fault-finding games for practice, and a novel means for assessing the success of our teaching tools.

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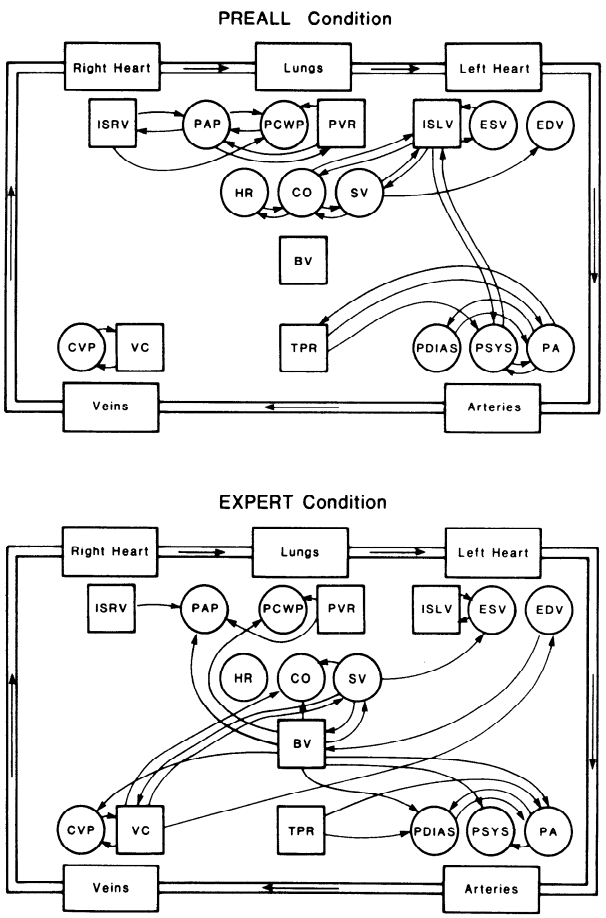
Representation of Integrative Thinking

The key to evaluating the success of instilling in students a specific mental construct is in the ability to represent mental constructs of knowledge. Figure 1 portrays a representation of mental models of the cardiovascular system as held by knowledgeable but inexperienced students (panel A) and by experienced cardiovascular scientists (panel B). These models were constructed by analyzing responses to a questionnaire where the subjects were asked to rate the predictability of a cardiovascular property or variable when given information about another. Seventeen properties and variables were considered and the predictabilities of all 17 were rated with respect to each other for a total of 272 predictability scores. Figure 1 contains just the top 10% of these ratings, i.e., it shows the



Comparison of strongest 10% of predictability ratings: top (students), bottom (experts).

strongest connections between cardiovascular elements.

Experts and knowledgeable students differ in striking ways. The students made their strongest connections between items within an anatomic structure or between adjacent structures. There were no strong connections that linked the various system components. The student's view may be characterized as disjointed or non-integrated. On the other hand, experts made strong connections between all system components. Their view may be characterized as richly connected or integrated.

An effective method for teaching physiologic integrations would be one that moved the students from their disjointed view to a more integrated view as demonstrated by the experts.

Fault-Finding Teaches Physiologic Integration

Problem solving is often used to help students think integratively about physiology. We created a novel, computer-based problem-solving instrument in which faults were introduced into a simulated cardiovascular system and the students were asked to identify these faults by obtaining information about the system's performance. The objective was to identify the fault with a minimum amount of information and without making wrong guesses. There were 28 possible faults which were chosen at random. The students were asked to solve these randomly chosen faults 50 times. The students had previously completed the standard first-year medical physiology course. It took, on the average, 5 hours to solve the 50 faults.

The predictability rating task was administered to the students both before and after the fault-finding exercise. The top panel in figure 1 gives the results prior to the fault-finding test. Statistical analysis was applied to both the pre- and the post-fault-finding mental models. The results were that the post-test mental model was significantly more like that of the experts than the pre-test mental model. From this evidence we judge that the fault-finding exercise was effective in teaching physiologic integrations to these students. A detailed report of these findings can be found elsewhere (1).

Explicit Teaching of Physiologic Integrations

We view the fault finding task as an indirect approach to teaching physiologic integrations. We are interested in developing explicit methods of teaching integrative thinking about physiologic systems. We have previously developed a series of simulated laboratories with the aim of demonstrating organ system behaviors (2). In a new computer program the laboratories have been designed to work together, sharing parameters and data. For example, a cardiac function curve and venous return curve may be created and plotted together. Data from the full cardiovascular system model may also be plotted and will be seen to lie on the intersection, confirming the system operating point, figure 2. This program presents physiologic knowledge in a structured fashion which emphasizes the hierarchical features of the cardiovascular system. It includes an emphasis on system dynamics as an integral part of physiologic function. A description of the program can be found elsewhere in this journal (3).

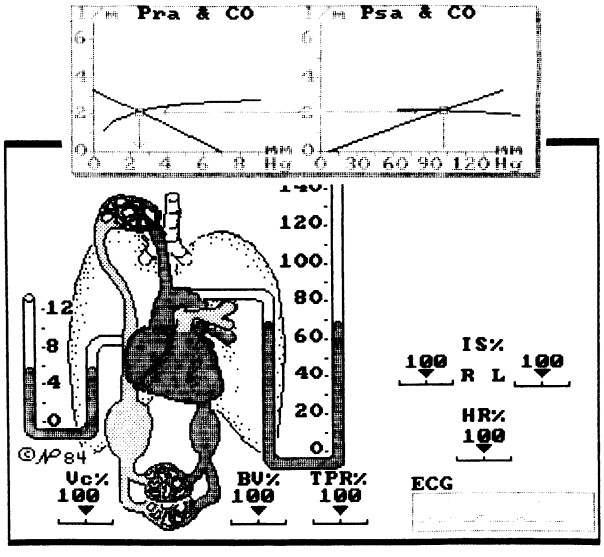


Figure 2. Data from experiments in heart-lung and systemic circulation laboratories and whole system operating points.

A future goal is to compare the efficacy of indirect fault-finding methods with the direct dynamic systems approach in teaching students to think integratively about physiology. In doing this, we will rely heavily on assessments of mental models in both students and experts. We suspect from our early experience that each method will be effective, but that a combination of the two will result in a synergism that will yield best results.

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COMPUTER SIMULATION OF QUANTAL DOSE-RESPONSE RELATIONSHIPS

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A microcomputer program was written to simulate animal pharmacology experiments involving "all-or-none" responses. The program may be used as a teaching aid to reinforce the concept of the dose-response relationship in pharmacology. The program is based on the premise that individual animals vary in their sensitivity to drugs according to a normal distribution. The student selects a drug action from a list of 10 items. He then chooses the doses to be administered and the number of animals to receive each dose. Each animal's response is based on random variation about a standard dose-response curve obtained from published experimental data. At the conclusion of the simulation, the student may calculate the ED50 and slope and their 95% confidence limits by hand or using available computer programs. New drugs and actions may be easily added to the program. Repeated testing of the simulation has supported its statistical validity. Use of this program in a pharmacology teaching laboratory provides students with a rapid and economical way to gain experience in the design and statistical analysis of quantal dose-response experiments.

Introduction. In the teaching of the biological sciences, it is useful for students to become familiar with experimental data so as to gain insight into the principles of biological variation, experimental design and statistical analysis. Experiments involving quantal or "all-or-none" responses are of special interest to the pharmacologist and toxicologist. In toxicological studies, for example, experiments are performed in which the endpoint is death. The percent of animals killed will vary depending on the dose of drug given. The median lethal dose (LD50) and its confidence limits may be estimated by probit analysis or other methods (3,6). The best way to gain knowledge and experience with quantal data is to perform animal experiments. However, these experiments are costly in dollars and time are criticized by some as wasting animal resources (4). The ED50 SIMULATION program was written to provide students with an opportunity to design and perform simulated quantal dose-response experiments on the microcomputer.

The Program. ED50 SIMULATION is based on the premise that individual animals vary in their sensitivity to drugs according to a normal distribution. The student selects a drug, species and action from a list of 10 items:

	DRUG	SPECIES	EFFECT
1.	Morphine sc	Mouse	Lethality
2.	Levorphanol ip	Mouse	Lethality
3.	Morphine ip	Rat	Lethality
4.	Cocaine iv	Rat	Lethality
5.	Procaine iv	Rat	Lethality
6.	Morphine sc	Mouse	Analgesia
7.	Levorphanol sc	Mouse	Analgesia
8.	Codeine iv	G. Pig	Antitussive
9.	Dextromethorphan	G. Pig	Antitussive
10.	Alfentanil iv	Man	Anesthesia

He then chooses the doses to be administered and the number of animals to receive each dose. The computer randomly assigns to each animal a position on the cumulative normal distribution curve representing the animal's relative sensitivity to the drug. The program contains the equation of a standard dose-response curve for each drug. On the basis of the standard curve and each animal's relative sensitivity to the drug, a decision is made by the computer whether or not the animal responded. The proportion of animals responding at each dose is tabulated:

DOSE OF MORPHINE	PROPORTION DEAD	PERCENT DEAD
300	2/10	20
500	4/10	40
800	9/10	90

The student uses these data to estimate the LD50 and slope and their 95% confidence limits by hand (3,6) or using available computer programs (5,7). Each standard dose-response curve is based on published experimental data (ref. 1,2 and others). The instructor can easily add more items to the list.

Methods. To test the ED50 SIMULATION program, 5 different simulated morphine lethality experiments were run 100 times each. The number of doses per experiment ranged from 3 to 5 and the number of animals per dose ranged from 5 to 20. The slope and 95% confidence limits were determined by probit analysis (3) using a BASIC computer program (5). For each simulation, one of three outcomes was possible.

1. An LD50 and 95% confidence interval were computed.
2. No confidence interval was computed because the slope of the dose-response line was not significantly different from zero.
3. There were not enough points (excluding 0% and 100% responses) to make a first approximation of the dose-response line.

The second and third outcomes were considered failures, since no meaningful data were obtained.

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Results and Discussion. For the simulation to be valid, one would expect each of the following criteria to be satisfied:

1. The median LD50 and slope of a large number of independent simulations should approximate the "true" LD50 and slope of the standard dose-response curve.

2. The 95% confidence limits of the experimental LD50 should include the "true" LD50 about 95% of the time.

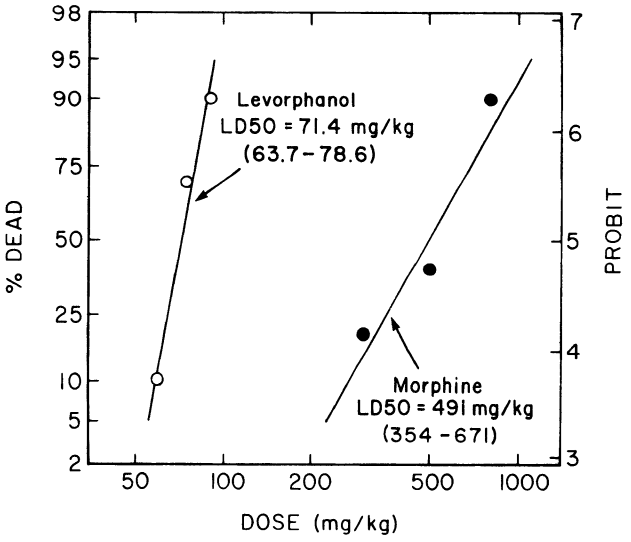

Fig. 1. Computer simulation of morphine- and levorphanol-induced lethality in mice. Ten mice were tested at each dose. "True" LD50's based on published data (1,2) were 71.3 and 452 mg/kg for levorphanol and morphine, respectively.

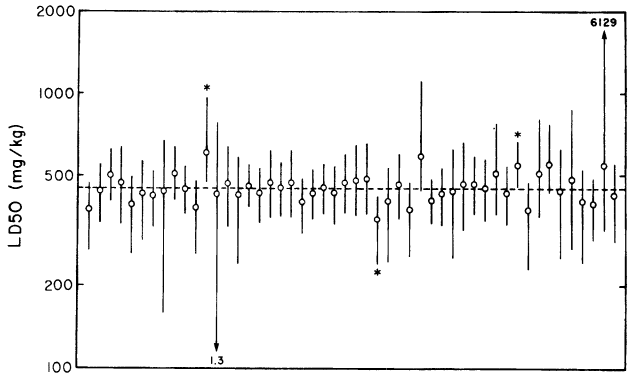

Fig. 2. LD50's and 95% confidence intervals from 50 consecutive simulations of morphine-induced lethality in mice. Each simulation consisted of 4 doses, with 10 mice per dose. Asterisks indicate 95% confidence intervals which did not include the "true" LD50 of 452 mg/kg.

Figure 1 shows simulated dose-response curves for morphine- and levorphanol-induced lethality in mice. In both cases, the experimental LD50 was not significantly different from the "true" LD50. When LD50's and 95% confidence intervals were determined for a series of 50 repeated simulations, 96% of the simulations included the "true" LD50 within their confidence limits (Fig. 2).

TABLE 1

Number of Doses	Number of Mice per Dose	Median LD50 (mg/kg)	Median Confidence Interval	Failures per 100 Simulations
3	10	454	276	19
4	10	444	230	5
5	10	447	209	4
4	5	444	407	42
4	20	441	150	0

Table 1 summarizes the results of 5 different morphine lethality experiments. Each simulation was run 100 times. The median LD50's and slopes (not shown) were very close to the "true" LD50 and slope. These data support the validity of the simulation program. Increasing the number of doses or increasing the number of animals per dose decreased the failure rate and reduced the size of the 95% confidence interval.

Use of the ED50 SIMULATION program in the pharmacology teaching laboratory provides students with a rapid and economical way to gain experience in the design and statistical analysis of quantal dose-response experiments.

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ED50 SIMULATION was written in Applesoft BASIC for use in any of the Apple II computers and is available from the author. To obtain a copy, send a blank 5.25" disk and indicate whether or not your computer has 80-column capabilities. The disk will be returned containing the ED50 SIMULATION program, a companion program for analyzing quantal dose-response experiments (5) and instructions for adding a new drug to the ED50 SIMULATION program.

TEACHING DIAGNOSIS BY COMPUTER

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The diagnostic process, which at first appears simply to be the matching of patient findings to disease manifestations, turns out to be considerably more complex because of medication or concurrent disease in the patient as well as variability of disease manifestations because of variants or stages in the disease. These complications coupled with the expressing of both patient findings and disease manifestations in the natural language phreaseology of the clinician makes the matching process too complex for capabilities of the microcomputers generally available today. The matching task can, however, be simplified if there is standardization (and hence coding) of the phrases used to describe patient findings/disease manifestations.

There are six types of medically-significant events that are common to both patient findings and disease manifestations, namely: agents (A); clinical findings (C); diseases (D); extraclinical tests (E); modifiers (M); and procedures(P). Of these types of events, two (D and P) already have codes assigned to them through the ICD.9.CM (International Classification of Diseases). A third type of event (P), is close to definitive code assignment through the American Hospital Formulary Service. I have devised codes for C, E, and M.

After I have coded a series of diseases and written (in the C language) the necessary programs, the third year medical student can first ask to see the manifestations (A,C,D,E,M, and P) associated with any of the diseases available in the microcomputer data base. Moreover, the student can then ask which of these diseases displays a particular manifestation such as cough or elevated serum creatinine. The neophyte clinician thus begins to think like a diagnostician in matching manifestations of various diseases to findings on a particular patient.

In my COMPARE (Compatible Patient Records) system, a patient's medical record is a chronological series of events (A+code, C+code, etc.) preceded by the time of occurence of each event. A patient record in this format can be interacted with the coded lists of disease manifestations, to see which diseases have most similarity to the findings on this patient, a first approximation of computer diagnosis.

In the early stages, the computer system will be much too naive to be useful in any real diagnostic situation but can be gradually improved by adding: 1) probability considerations such as occurrence of a particular finding in a disease (sensitivity); 2) mechanisms for discounting the effects of concurrent diseases or medications; and 3) recognition of disease variants, stages, and the temporal development patterns of diseases.

Diagnostic success at various stages of development of the computer diagnostic system can be evaluated. As the computer achieves reasonable reliability on actual patient records, the seasoned clinician may wish to match wits with it, particularly since he may be reminded of diseases which he encounters infrequently.

A real impediment to the use of the computer for patient records or diagnosis is the mode of input of patient data by the clinician. At present, my system utilizes menu presentation on an IBM PC, with keyboard responses. Perhaps the newer microcomputer modalities of windowing and the mouse will provide a more adaptable approach for busy clinicians who don't want to type on a keyboard.

Clinicians not happy with rigidly standardized phraseology may be willing to pay extra for a preprocessor for the system that will accept a variety of natural phrases and translate them into the standard coding required for the microcomputer diagnostic matching system.

Note should be taken of the fact that the six event files (A, C,D,E,M,P,) are independent of the computer program for diagnosis or the computerized patient record and hence these event files can be expanded to supply considerably more detail which may be used for a different purpose. For example, the Extraclinical Test (E) file can be amplified to include nature, precautions, indications, and limitations of the tests as well as reference intervals ('normal' values) and sensitivity in various diseases. The Clinical Findings (C) file can expand to include mode of observance, 'normal limits', and diseases associated with abnormalities. The Diseases (D) file can encompass clinical findings and extraclinical tests that are abnormal for each test. Thus a wealth of detail is available in the total computer data base.

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RESPSYST: An interactive Microcomputer Program for Education.

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ABSTRACT

RESPSYST is written in BASICA for use on an MS-DOS or PC-DOS microcompu-ter and incorporates more than 20 of the factors that determine gas transport by the cardio-respiratory system. The program includes a discussion of most of these factors, a few question and answer sections, and relies heavily on graphics to demonstrate the interrelationships between different parameters. The program consists of five major parts, which are: ALVEOLAR GAS; DIFFUSION; HEMOGLOBIN SATURATION; VENTILATION/PERFUSION and HYPOXIA. The last section incorporates all of the variables introduced in the earlier subroutines and allows the user to alter 12 parameters to examine the overall effect on gas delivery. The program also includes patient data which define typical changes present in several common respiratory dysfunctions. This program was used in several physiology courses as the framework for a laboratory experiment, as a conference aid to demonstrate various interactions, or as a means of projecting dynamic slides in the lecture room to a large group of students.

Description of the Program

RESPSYST is completely menu driven so that minimal computer knowledge is required to use the program. RESPSYST begins with an overview of the interactions of the major factors determining gas transport. The user is then presented with a menu and may choose any of the five main portions of the program, which are: ALVEOLAR VENTILATION, DIFFUSION, HEMOGLOBIN SATURATION, VENTILATION /PERFUSION or HYPOXIA. Each section of the program requires 15-30 minutes to complete, so that students may stop and later begin a new section without having to repeat already completed work. The text portion is kept to a minimum so that the program functions best as a review of the material rather than as the primary source of information. There are several sections of question and answer format in the program. If students enter an incorrect answer the program returns to the appropriate screen so that the information can be reviewed.

The ALVEOLAR VENTILATION section of the program uses the alveolar gas equation as the framework for presenting the material. Each of the parameters in the equation is discussed briefly. The PCO_2 is discussed in the context of factors that alter alveolar ventilation (tidal volume, frequency and dead space). The user can then view the relationship between PAO_2, $PACO_2$, and alveolar ventilation as a function of barometric pressure, fraction of inspired O_2, respiratory frequency or dead space/tidal volume ratio (Figure 1).

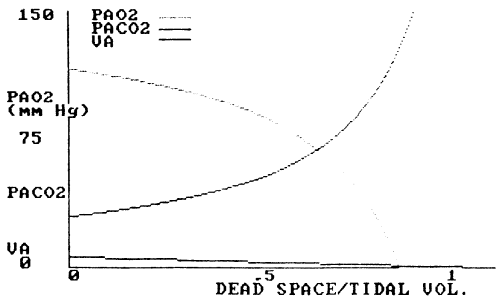

Figure 1. A graphics screen is depicted from the alveolar ventilation section of the program. The lines are readily distuinguished on a color graphics monitor.

The DIFFUSION section of the program provides a discussion of the Fick diffusion equation and derives the diffusion capacity equation. Six parameters are identified that determine the rate of diffusion. These parameters are: alveolar PO_2, diffusion capacity of the lungs, pulmonary blood volume, cardiac output, hemoglobin concentration and the P_{50} of hemoglobin. These parameters can be altered singly or in combination and the effect on diffusion can be examined by means of a graph of pulmonary capillary PO_2 as a function of time in the pulmonary capillary. Multiple runs can be superimposed on the same graph if desired (Figure 2).

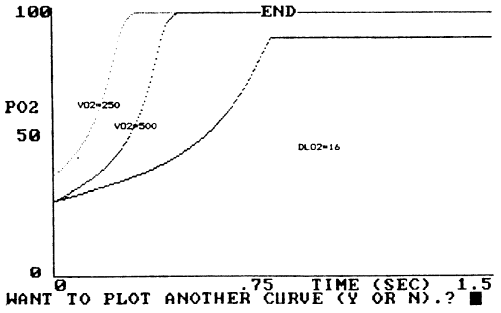

Figure 2. A plot of pulmonary capillary PO_2 as a function of time in the pulmonary capillary. DLO2 is diffusion capacity of the lungs; VO2 is oxygen consumption.

The HEMOGLOBIN SATURATION section begins with a brief discussion of the terminology and then provides a graph of the O_2-hemoglobin dissociation curve. The user can alter hemoglobin concentration, pH, PCO_2 or temperature to observe the effects on O_2 capacity and the P_{50} which are calculated for each curve. The hemoglobin dissoc-

iation curve is calculated by means of a linearized version of the Hill equation. As above, multiple plots can be superimposed on the same graph (Figure 3).

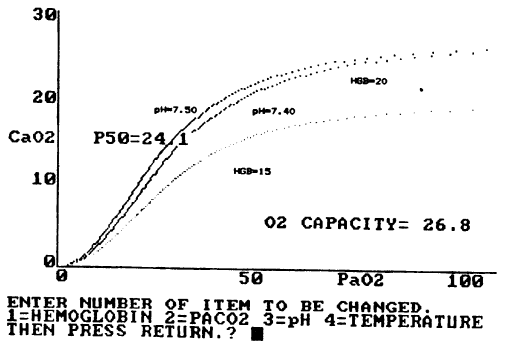

Figure 3. Hemoglobin saturation curves showing the effects of altering pH and hemoglobin concentration.

The VENTILATION/PERFUSION section of the program uses a version of the shunt equation to identify factors that determine the effect of shunted blood on the arterial O_2 tension and O_2 content. The student can then see tabular data of blood gas composition as a funtion of PaO_2, shunt fraction, hemoglobin concentration, O_2 consumption, etc.

The last section of the program, HYPOXIA, utilizes 12 independent variables which were introduced in the previous sections and calculates a large number of dependent parameters. These parameters include alveolar ventilation, alveolar, arterial and venous gas tensions, diffusion time in the lungs, and arterial pH and bicarbonate concentration. These values are presented schematically as a respiratory acinus and its associated blood supply (Figure 4). The HYPOXIA section of the program has proven to be most useful in either a laboratory, conference or lecture setting to demonstrate a wide variety of conditions. This part of the program also includes data from typical patients with respiratory distress syndrome, restrictive lung disease, chronic bronchitis and emphysema. This data can be used to demonstrate the effects of these diseases on the gas transport properties of the body.

Discussion

Computer modelling is being used more frequently to replace laboratory experiments in many science curricula. Until the educational value of this method of teaching is validated it is necessary to proceed intuitively, based on previous teaching experience, to try different methods of presentation. This program has been used to demonstrate gas exchange relationships for several classes of medical students and a graduate course for environmental engineers. Reaction to the program has been positive and, as judged by the response on questionnaires, the students find the program most valuable for independent study. I feel that the best use of the program would be if groups of 4-6 students investigated the program with some minimal direction provided in a handout. Faculty should be available to provide help if required. The students should design experimental situations and utilize the program to answer questions which are raised by independent exploration of the factors involved in gas exchange. Motivated and knowledgable students would probably obtain the most benefit from this type of study.

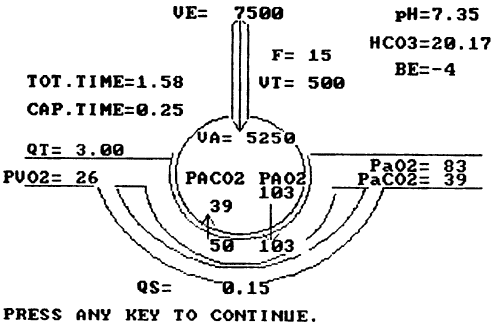

Figure 4. A respiratory acinus from the hypoxia section of the program. The results which are depicted are due to a decrease in cardiac output (QT).

This program can provide students with practice in problem solving and deductive reasoning which are so important in clinical medicine and the research laboratory. The use of patient data also allows students to identify the pathophysiological mechanisms and attempt to compensate for the disease process by altering the appropriate physiological parameters. This use provides one of the chief benefits of patient simulations since students can experiment on the model without causing harm. In addition, the response of the computer program can accelerate the disease process or speed up the effects of treatment so that the student can more readily appreciate the effects of the intervention.

The RESPSYST PROGRAM is available from the author by sending a blank double sided/double density soft sectored diskette in a stamped-self addressed envelope to the above address.

A COMPUTER SIMULATION of the INTERACTION of DRUGS with CARDIOVASCULAR REFLEXES

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[abstract] The University of Texas Medical Branch (UTMB) has experimented with the application of mathematical models--in the form of microcomputer programs--to teaching physiology and pharmacology. The primary motivation comes from long range cost savings because the programs not only reduce or eliminate the need for animals, recording instruments and other equipment purchases may also be sharply reduced. Such economy would be specious, however, if the quality of learning were compromised. After two years of exploring the strengths and weaknesses of computer models, we have come to recognize that one of their most promising qualities is that they permit the conduct of experiments which, for practical reasons, cannot be performed in the teaching laboratory. Examples include experiments which involve the measurement of hormone or drug levels, membrane potentials or peripheral resistance. In addition, simulations are more effective when they involve the student as a participant rather than an observer. A simulation which will not progress without student interaction forces the student to think about what he is observing. We have now had the opportunity to evaluate the first of several programs which incorporate these principles. The combination of the simulated experiment, dealing with the pharmacological aspects of regulaton of the circulatory system, together with a non-graded oral quiz on the material has increased examination scores by ten points compared both with previous years and with other exam scores of that class.

At UTMB, we have experimented with computer simulations of animal systems in the medical student laboratory for the past three years. The thrust of our early efforts was simply to acquire the appropriate hardware and to obtain usable software either from others working in this area or by writing it ourselves. With several satisfactory, if not ideal, simulation programs on hand we have paused to examine their individual strengths and weaknesses. Our objectives are: 1. to determine where to replace animal experiments with simulations and where animal experiments should be retained; 2. to produce new simulations to strengthen topics which traditionally have been under-represented in the student laboratory; 3. to identify those aspects of the simulations which enhance learning so that they can be exploited.

The simulation with which we have had the most experience and which we feel is most successful mimics the circulatory system, the portion of the autonomic nervous system which regulates it and part of the pharmacology of the peripheral effector organs. We call it "CVREX" for cardiovascular reflexes. Most of the comments made here the result of our experiences with this simulation.

ADVANTAGES of COMPUTER SIMULATIONS

The most important consideration in the determination as to whether any change is to be introduced into a curriculum should be: Does the proposed change improve the quality of instruction? Computer simulations do not, necessarily, constitute a better learning environment than traditional experiments. It is probable that simulations will be superior, however, because they do not suffer from many of the limitations inherent to animal experiments.

Vying with improvement in learning for first place on the advantage list is financial savings. While they are not inexpensive, microcomputers (or personal computers, or PCs) are usually more economical than animal experiments. There are several reasons for this. Physiological instrumentation tends to be specialized. If one wishes to add a new experiment to the curriculum, it often entails the purchase of additional--and usually expensive--equipment. The cost of animals continues to rise and often salaries must be paid to those who care for and prepare animals. When one takes into consideration the fact that simulations replace instruments as well as animals, the cost factor is usually strongly in the favor of simulations.

There is another aspect of the fiscal saving which should be emphasized. Until now, mammalian physiology laboratories taught at undergraduate institutions were often inadequate unless the university was wealthy or the instructor was especially resourceful (or both). Sentiment against animal experimentation on the part of school officials may also be involved. Computer simulations can expand the range of laboratory activities available to undergraduate schools to include exercises previously available only in professional institutions. As a bonus, when laboratories are not in session, faculty and students may use the computers for data analysis or as word processors on which papers may be written.

A third advantage of simulations stems from the fact that animal experiments often yield incomplete data. A well known example concerns the circulatory system. Students measure pressures at many sites in the vasculature but seldom is bloodflow measured. There is a very good reason for this, of course: bloodflow is difficult to measure in the student laboratory. It is, however, like teaching physics with voltmeters but no ammeters. It is a serious omission and I am convinced that many students leave the laboratory with the impression that pressure is somehow more important than flow. Computer software which simulates a circulatory system must generate flow data and it is a simple matter to display these values. The ability to demonstrate which way cardiac output changes or that it does not change under a given set of circumstances goes a long way towards helping the student understand the circulatory system. There are many other examples of animal experiments which produce inadequate data. Furthermore, there are many more possible experiments which have never been introduced because the necessary instruments or transducers are too expensive, too difficult for students to master in one afternoon or do not even exist. Physiologists and pharmacologists who write simulated experiments will have to adjust to a world where "permeability transducers" and "gastrin meters" are as possible as pressure transducers.

An animal experiment, no matter how well designed, may on occassion, yield faulty data. Pound animals, may display anomalous responses because of parasites or other pathological conditions. Students like to quip that the animal did not read the book. There are times when these deviations can be instructive, however when one is attempting to learn basic principles they are distructive. A well-written simulation will always be consistant with texts and lectures.

Presented at the Learning Resource Center at the 69th Annual Meeting of the Federation of American Societies for Experimental Biology, Anaheim, California April 22-25, 1985.

Computer simulations ease scheduling constraints. In the case of animal experiments, one-half day is usually set aside for the experiment to be conducted. Special arrangments must be made for students who are absent. With animal experiments this can pose serious problems. Simulations may be conducted at any time and may even be interrupted to attend another class if necessary Furthermore, parts of an experiment dealing with a concept which is not fully understood may be repeated. Perhaps most important of all, errors may easily be corrected. The possibility of a student making a particular error can be ruled out by the programmer or, where there are instructional benefits to be derived, the potentiality for making an error can be included. The professor who has seen a student section the carotid artery instead of the vagus nerve will appreciate this.

In an attempt to increase the flexibility of the CVREX simulation we inadvertently increased its effectiveness as well. The protocol includes many junctures at which the student must indicate what he wants to do next. Because he must make a decision every few minutes, he must constantly keep his thoughts on the experiment, analyse his observatons and plan his next move With the student managing the experiment rather than simply observing it, the simulation runs 50% faster than its animal counterpart and we are convinced that he learns more.

DISADVANTAGES of SIMULATIONS

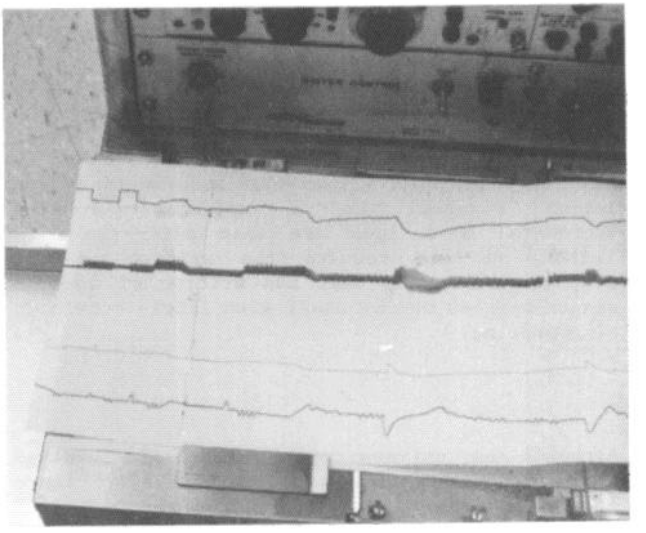
The major drawback we have encountered has been that certain simulations are deficient in some, seemingly irreparable way. For example, the study of the properties of skeletal muscle is more effective using a frog gastrocnemius than as a simulation. The simulation will do what the in-vivo experiment will, but the model seems contrived. We could write a program illustrating the events which take place during cardiac systole but we feel that the animal experiment has more educational value. Any experiment which attempts to teach techniques, anatomy, or familiarity with equipment or procedures is likely to be a poor candidate for simulation. This is not a hard and fast rule,however.

Another class of experiments which are not good candidates for simulations are those which can involve the students as subjects. Simulations could be written for teaching basic electrocardiography, stress testing and respiratory function measurements but they would be inferior. This is due, in part to students' interest in themselves and their bodies. In addition, it is appropriate preparation for clinical studies.

Some clinical faculty have expressed fears that the simulations may "dehumanize" medical education by training students to place more faith in what they find in a computer read-out than in their direct observation of the patient. They see two problems: Students may miss important diagnostic clues that they could only obtain by observing or talking with the patient. The second potential risk is that they may devote so much time to examining data sheets that the patient begins to feel that he is being ignored. Animal welfare advocates, on the other hand, argue that the simulations free students from dehumanizing animal experiments.

Faculty attitude is always an important aspect of teaching and seems to be even more important when simulations are used. No matter how poor an animal experiment is, it is "real." And, no matter how well a simulation is written , it is not. Some people trained as scientists cannot take seriously something they regard as fictitious, including simulations. An instructor with this bias may either refuse to participate or may sabotage the experiment. The latter is the more serious case. The person assigning faculty for laboratory teaching must be prepared to deal with this complication.

It is our position that the greatest value of simulations is that they allow the student to try-out his understanding of how a system works in a way which is seldom possible with traditional student laboratory experiments. If the model does not behave as he predicted, he knows where to look for the source of his misunderstanding and he can then take measures to correct it. As one student put it to me, "I was not aware that I didn't understand this material until I worked with this simulation."



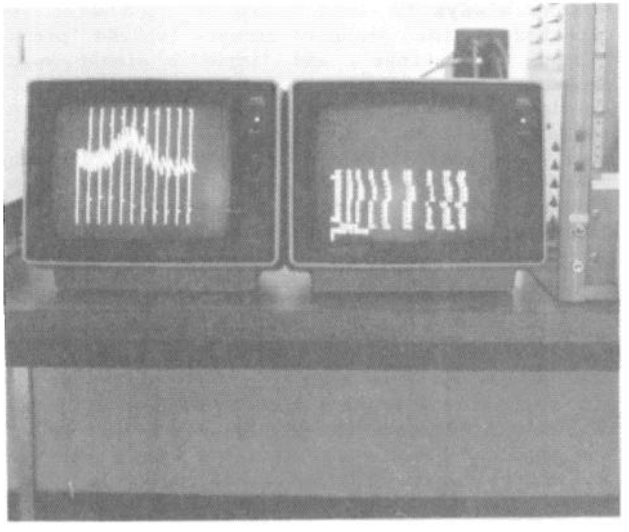


Figure 1 (left) Simultaneous polygraph-type graphic readout with tabular presentation of data generated by the CVREX program Continuous excursions represent arterial pressure. Vertical lines mark six second intervals. Small marks on time lines pointing left indicate TPR; those pointing right are cardiac output.

Figure 2 (above) By means of digital to analog converters, computer generated data can be recorded on a polygraph producing a record very similar to that from an experimental animal. Channels are: (top) TPR, arterial pressure, myocardial contractility and cardiac output.

THE USE OF A COMMON DRIVER FORMAT FOR C.A.I.

M.E. JONES, J.W. MANN AND M. AUCONE.

THE FLINDERS UNIVERSITY OF SOUTH AUSTRALIA

Exchange of computer-assisted-instruction (C.A.I.) material between institutions is often impeded by incompatabilities of hardware, software and curriculum. This seriously decreases the cost-effectiveness of C.A.I. because the cost of mounting new lessons can usually only be offset by the benefit gained by the small number of students within the author's institution. The use of a DRIVER programme allows each lesson to be defined by two files (text and logic) in a form which is independent of the hardware on which it is to run. A single DRIVER program, written once for the hardware in any language, then allows that machine to accept lesson material in a universal format. Incidental advantages are that alterations to lessons do not require the writing of new computer code, and that the writing of lessons can be carried out by staff with little knowledge of computing.

Although many university departments are involved in computer assisted instruction (C.A.I.) there has been only very limited interchange of material. Commonly, the material available has been written 'in house' by a few interested faculty. These early lessons are often 'hard coded'; the lesson is a computer program; a new lesson corresponds to a new program. It makes no educational difference how the lesson is made to appear on the screen providing its content and sequencing is educationally sound, but the time comes when the 'behind the scenes' details of programming are important: the topic advances and the lesson must be updated; the curriculum changes; the old mainframe is belatedly decommissioned in favor of new micro-computers. When this happens, a suite of poorly documented lessons hard-coded in an unfamiliar dialect by a long-departed programmer represents wasted effort. It is too difficult to resurrect, alter, and remount the lessons on new hardware.

Driver programs overcome these problems and have been developed for many years. They are commonly used to allow libraries of multiple choice questions (MCQs) to be run masquerading as C.A.I. Because MCQs are all of a similar format it is possible to have the MCQs and their answers on a file, and to write a program to administer them. A new set of MCQs can be prepared for the students by preparing a new file. Importantly, this requires no new computer programming; the same driver program administers a new lesson by accessing a new file. The educational value of MCQs is often questioned, but that is not the issue here. The important issue is that by limiting the format of the questions it is possible to separate the content of the lesson (here, a file of MCQ questions) from the programming necessary to present the lesson (here, the 'driver program' that acceses the file). Although such a strategy limits question format, a driver is not limited to any one format. There are, however, so few formats in common use that a simple driver handles them all. Already a variety of drivers are in use and it is opportune to discuss the features which might be desirable for drivers administering C.A.I. material in the life sciences. The use of a driver facilitates the writing and update of lessons, interchange between dissimilar hardware, and the monitoring of student use. Disadvantages include some limitation of format and of graphics.

The usefulness of common driver programs to facilitate the exchange of lesson material will be enhanced if there are a few, widely distributed drivers. A multiplicity of drivers doing almost the same things in very different ways would probably create a situation worse than no drivers at all; a situation in which C.A.I. libraries contained nearly as many drivers as lessons. The scenario is perhaps extreme, and is best avoided by publicizing what is available in the hope that others using drivers will do likewise, and that still others about to enter the field will become familiar with an appropriate available driver rather than creating a new one. In discussing the characteristics of the Flinders driver, we feel that it is important to say not only what it does but why; a driver can be made to do anything but the set of useful characteristics is defined by the educational objectives.

Obviously a driver must be capable of putting text on the screen, but perhaps less obviously it is of benefit to divide the usual 25-line screen into three areas which can be controlled independently. We always leave the bottom line as a 'prompt' so that the student learns always to look there to find what is expected of him. Standard prompts include 'press RETURN to continue', and 'input a single word answer'. The remaining 24 lines are divided into an upper 16 and a lower 8. The driver can refresh the lower lines while leaving the upper ones unchanged. This is particularly useful when correcting a wrong answer, often the result of a student having misread (or misunderstood) the question. If under those circumstances the misunderstood question is erased, the ensuing explanation makes no sense. When the bewildered student recognizes that he may have mis-read the question, it is important that it still be there for re-reading.

Naturally, the sequencing of a program is not everywhere dependent upon student input; two of our six 'formats' simply allow for refreshing the upper or lower areas from the text file with the prompt 'press RETURN to continue'. It is of course the branching of a program as a function of student input which contributes to the

usefulness of C.A.I. It is the variety of ways in which this branching may be accomplished that determines whether a driver will do what the author of a lesson would wish. In general, we have found that four types of question allow for all that our academic authors ask. One of these is the MCQ question with which readers will be familiar and we will not discuss it further. Two further question types represent a binary choice in terms of question branching. In each case there is a set of student responses defined as 'on target' and which lead along one program branch. Any other response leads along the alternative branch. The 'on target' set can be defined in a variety of ways; it can be a number plus or minus a percentage, it can be a letter,or it can be 'free format'. In the latter case a single word answer is requested and this is compared to a pre-defined set comprising the 'on target' answers.

The binary branch format above is 'static'; 'on target' answers are the same whenever the program is run. For numerical questions, students tend to 'swap' the right answer without swapping an understanding of how the right answer was arrived at. This is overcome in a second format, limited to numerical problems, in which the right answer differs each time the program runs. An example might be to calculate a time constant given a half-life. The driver selects a half-life at random from a given range, supplies that half-life to the student in the question and calculates the time constant which will be considered 'on target'. Students can thereby swap the method by which the right answer is obtained, but they cannot merely swap a number.

Questions are often such that answers cannot simply be characterized as right or wrong, and thus leading to a binary branch in a program. A student may be given a range of options with a different branching of the program for each option. While it is logically possible to have more than two branches in response to letter, number, or 'free format' answers, this is cumbersome to program. We have restricted multiple branching to questions in which the answer options have been enumerated, rather like an MCQ. It differs from the MCQ format, however, in that there is no constraint on the number of options offered, but only one may be chosen.

We have found it useful to be able to score answers on two different scales. These may represent factual knowledge and judgement, or time in hospital and the cost of diagnostic tests. The driver can independently add to or subtract from both scores.

We use a 'flag' facility. The flag can be set up, down or unchanged on entering or leaving a question. At each branch point, the destination can be determined not only by the student answer but also by the status of the flag. This is convenient when a student's wrong answer has been followed by an explanation and a second attempt at the same problem. Judicious use of the flag prevents the poor students from moving forever around the same loop. Under these circumstances we usually use the flag to direct the student to log off and seek the personal help of a tutor. Often, however, the student wants yet another attempt at the problem. This raised a philosophical issue; in writing the program we determine what we think the student should do, and the sequence in which he should do it. What happens if the student wishes to return to an earlier part of the lesson, or if we want to stop the lesson while he wants a third try at a failed question? Our approach has been to allow the student temporarily to remove sequencing control from the driver and then either to stop the lesson, re-attempt the last question, or reposition himself at any point in the lesson. This facility met with an enthusiastic response from the students, and we have not regretted introducing it.

Technical details of the Flinders driver are available from the authors on request. We are happy to provide a list of lessons currently used at The Flinders University of South Australia.

Dr. Sanger's Apprentice

A Computer-Aided Instruction to Protein Sequencing

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Abstract

Modeled after the program "Mastermind", written by Steve Sontum and Steve Daubert, "Dr. Sanger's Apprentice" teaches students the art of protein sequencing. The program generates a polypeptide whose sequence and length can be user-defined (for practice) or computer-generated (for grading). The student's objective is to deduce the sequence of this polypeptide using many of the tools available to a protein chemist.

Instead of being given operations and their results, as in a textbook, the student specificies the operations and the order of their application. Success in determining the sequence depends on the student's understanding of the experimental procedures and on the logic in executing those procedures. Operations available range from simple enzyme digestions to complex analyses such as Edman degradation. The program mimics laboratory situations and places limits on the amount of peptide available for analysis.

Written in Turbo Pascal for the IBM PC, the program requires 128K, a graphics adapter, and an 8087 math coprocessor.

To work under and learn from a master craftsman has been the concept of an apprenticeship since the origin of the word in the Middle Ages. A student learns from the experience and method of the teacher and is afforded access to the tools the master originated and developed in perfecting his craft. Determining the linear sequence of amino acids comprising a protein (*i.e.* the primary structure), we view as a biological craft best learned from such masters as Nobel Laureate Fred Sanger. This clearly is not possible for all students. Moreover, protein sequencing has evolved into a highly technical field, requiring expensive instrumentation and hazardous chemicals. However, the tools and logic involved in this craft can be taught to students of science. We believe the microcomputer provides a unique educational forum for learning this and many other biological concepts. "Dr. Sanger's Apprentice", the subject of the first program in our "Apprentice series", gives the student many of the same powers, limitations, setbacks, and opportunities a protein chemist faces when determining the primary structure of a protein.

When we undertook the overall design of the program, we developed several ideas that we felt would make the program realistic, accurate, challenging, and still be interesting and, above all, teach the student the art of protein sequencing. Among these points are:

A strong sense of realism. Experimental errors and uncertainty combined with graphically produced data similar to test tubes and chromatographs serve to give the student a feel of both the ambiguity and complexity of real lab work.

An autonomous program. All aspects regarding the program are on disk -- the manual, help files, and operation explanations are available anytime during the program and can be viewed repeatedly. The program also minimizes the amount of hand-recorded data kept by the student, reducing it to just the sequence itself.

Originality and challenge. Each session produces a completely random peptide, up to 20**20 different 20 residue proteins can be created. This gives each student a unique problem and challenges him as an individual, yet utilizes a common solving technique. Through an active interaction with the material, the student is required to make logical decisions.

Provide a visual interface. The graphics and extensive windowing capabilities available with Turbo Pascal give the program an impressive user interface.

All of these aspects combine to make the program a unique and effective teaching tool. It requires the student to think through and understand the problem before he can create a solution, thus teaching in a more active rather than passive manner as is often the case with textbooks and page-turning computer exercises.

The program starts with the student entering his name, which is used as a file name for the storage and retrieval of a session's data, and choosing the type of protein he wishes to sequence. For practice, the user can enter his own polypeptide or automatically generate a random protein of a specified length. If the student wishes to do it "for real", the program creates a random peptide of either 15 or 25 residues, depending on the status of the student. From this point the program displays a menu of sequencing commands and a prompt to start the puzzle. A help file is online at all times. The first page of the file is produced along with the title and the remainder can be either read or ignored, depending on the confidence and experience

of the student.

There are basically three types of sequencing tools available to the user: hydrolyses, digestions, and sequence determination. Acid and base hydrolysis give the composition of the peptide as moles of individual amino acids, taking into account the instability of certain amino acids (e.g. tryptophan). To cleave the polypeptide there are available several common digestive enzymes such as pepsin, trypsin, and clostripain. Also available are mild acid hydrolysis and hydroxylamine cleavages. Mechanisms for these operations are available at any time through one of the menu commands, enabling the student to determine where an enzyme will cleave his peptide. Output is in the form of fragments, labelled by the student and stored in a library which can be viewed at any time. Any operation can be performed on a fragment created by a previous operation. Edman degradation, along with amino and carboxyl-terminal analyses, round out the commands available to the user. The Edman operation gives successive **N**-teminal amino acids, the output from the program being similar to the output off an HPLC column. For each cycle, peaks corresponding to the PTH residue, along with multiple peaks constituting the background, are displayed. After several cycles, the decreasing yield for the terminal amino acid blends into the background, limiting the number of residues that can be determined. **N**- and **C**-terminal operations help the student determine overlaps and the final sequence. As an added bit of realism, the original amount of sample is limited and each operation performed on the original fragment removes a percentage of the sample. If the student runs out of sample before determining the sequence he has effectively "lost" and must start again with a new protein.

Sessions are designed to last from 1 to 3 hours. If a student cannot complete the session in one sitting, the data from the current session is saved and can be retrieved later, enabling the student to continue from the point he left off. When the student has finished by correctly determining the sequence of the protein the computer automatically saves to a file the record of the entire session, the protein sequenced and amount remaining, and the student's name and course. This file can then be read by the instructor.

The protein sequencer is the first of several programs planned to comprise the Apprentice series. Other programs will include protein purification, enzyme kinetics, and recombinant DNA. A second version of "Dr. Sanger's Apprentice" is currently in development. The new version will have a more direct and attractive user interface and added peptide complexity, including options for disulfide bonds and circular polypeptides. The main idea inherent in all these programs is embodied in the master-apprentice relationship. Complex biological concepts that are either too costly or too time consuming to duplicate in the teaching laboratory can be simulated by the microcomputer.

Presented at the Learning Resource Center at the 69th Annual Meeting of the Federation of American Societies for Experimental Biology, Anaheim, California, April 22-25, 1985.

Announcements

Computer Applications in Medical Care

The Ninth Annual Symposium on Computer Applications in Medical Care will be held November 10–15, 1985, at the Baltimore Convention Center, Baltimore, MD. Tutorials, plenary sessions, panel discussions, demonstrations, and exhibits will be presented. Subjects include ambulatory and direct patient care, artificial intelligence and decision support, associated health professions, clinical and administrative support services, education, epidemiology, legal issues, medical imaging, networking and communications, nursing, quality assurance and risk management, and simulation and modeling. *Information*: Jan L. Compton-Ouska, SCAMC–Office of CME, GWUMC, 2300 K Street, NW, Washington, DC 20037. Phone: (202) 676-4509.

Faculty Fellowships in Health Care Finance

The Robert Wood Johnson Foundation's Program for Faculty Fellowships in Health Care Finance is offering fellowships for a year of advanced training and field experience followed by grants of up to $15,000 in support of a related research project in the following year. These fellowships are open to faculty in university programs and departments where there is a health care finance and health policy focus, as well as to professionals in health-related disciplines considering a career in teaching and research. Relevant backgrounds include health services and hospital administration, public administration, public policy, law, business, medicine, political science, and economics.

Fellowships begin in September at The Johns Hopkins Center for Hospital Finance and Management with an intensive study of the latest innovations in health care finance followed by structured field and research experience. Up to six fellows will be appointed. They will receive stipends equal to their salaries prior to entering the Program, up to $40,000 a year, plus fringe benefits and assistance with other costs associated with the fellowship year. The Program is being administered for the Foundation by The Johns Hopkins Center for Hospital Finance and Management.

Deadline for applications: January 20, 1986. *Information*: Carl J. Schramm, Director, Program for Faculty Fellowships in Health Care Finance, The Johns Hopkins Center for Hospital Finance and Management, 624 North Broadway, Baltimore, MD 21205. Phone: (301) 955-6891.

Monoclonals and DNA Probes in Diagnostic and Preventive Medicine

The International Symposium on "Monoclonal and DNA Probes in Diagnostic and Preventive Medicine" will be held April 8–10, 1986 in Florence, Italy, at the Palazzo dei Congressi. Session topics include DNA probes in diagnosis of inherited diseases, monoclonal antibodies and DNA probes in diagnosis of infectious diseases, oncology, and new trends. *Information*: Organizing Secretariat, Fondazione Giovanni Lorenzini, Via Monte Napoleone, 23, 20121 Milan, Italy. Phone: (02) 70.22.67 / 78.38.68.

Seminar on Addiction/3

The Seminar on Addiction and the Jellinek Medical Association of Great Britain will be sponsoring the Seminar on Addiction/3 in London, UK, March 1–9, 1986, at the Waldorf Hotel. The faculty will consist of many experts in the field of Chemical Dependency, both from the United States and the United Kingdom. *Information*: Seminar on Addiction, c/o Agency International, Inc., 3033 Maple Drive, N.E., Atlanta, GA 30305, or by calling Don Abrams at (404) 266-2200.

Symposium of European Society of Osteoarthrology

The XVth Symposium of the European Society of Osteoarthrology, "Articular Cartilage and Other Joint Structures in Relation to Loading and Movement," will be held June 25–27, 1986, in Kuopio, Finland. Themes include biology and properties of the articular cartilage and other joint structures, interplay between surgical and drug therapy, and other aspects such as new methods, biology of the joint, and repair or aging of articular structures. *Information*: Dr. Heikki J. Helminen, Managing Chairman, Dept. of Anatomy, University of Kuopio, P.O. Box 6, SF-70211, Kuopio, Finland. Phone: (358)(71) 162-473.

International Congress on Medical and Scientific Aspects of Cycling

The United States Cycling Federation and United States Olympic Committee Sports Medicine Council will sponsor an International Congress on the Medical and Scientific Aspects of Cycling, 22-24 August, 1986, in Colorado Springs, CO, immediately prior to the 1986 Cycling World Championships. The Program Committee is now soliciting papers relative to the following topic areas for presentation at this meeting: biomechanical aspects of cycling; physiological aspects of cycling performance; technology as related to cycling (equipment, facilities, aerodynamics, materials, etc.); injury prevention, treatment, and rehabilitation; and general medical aspects of cycling (drug control, effects of travel on health, etc.). Poster sessions may be scheduled in addition to regular sessions.

Information about program content/topics: Program Chairman, Edmund R. Burke, c/o U.S. Cycling Federation, 1750 East Boulder St., Colorado Springs, CO 80909-5760 (303/578-4565). *General information*: 1986 Cycling Congress, c/o Mary Margaret Newsom, Department of Education Services, USOC Sports Medicine Division, 1750 East Boulder St., Colorado Springs, CO 80909-5760 (303/578-4575).

Receptors and Reflexes in Breathing

A symposium on "Receptors and Reflexes in Breathing" in honor of Julius Comroe is being planned for October 1 and 2, 1986, at the University of Pennsylvania School of Medicine, Philadelphia, PA 19104. *Information*: Dr. S. Lahiri, Dept. of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.