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Editorial Views

Technology, Medicine and Man

THE PRESENT scientific era may well be called by historians one of the greatest scientific revolutions of all time. It is all inclusive and fast paced—undoubtedly, a resultant, largely, of the amazing advances in engineering and electronics going back at least to World War II. The invention of powerful instrumentation such as the electron microscope, the X-ray diffractometer, and the ultracentrifuge have allowed us to redefine, and to probe more deeply into, the fundamental particles of biology and to reconstruct our views of the plan of man and nature in the form of a Molecular Biology and even more specifically, a Molecular Genetics. There is now a great obligation for medicine to discuss disease processes in these terms and to begin the long, hard process of relating observed and pre-classified macroscopic phenomena to underlying microscopic intracellular processes.

At the same time, another whole class of instrumentation has been developed in the form of high-speed electronic computers that provide man with the tools to aid in the process of analyzing, classifying and correlating vast amounts of data produced by these new explorations and, in a certain sense, in extending man's intellectual processes into realms which previously posed insurmountable obstacles of mathematical complications and intractabilities. And most recently, computers have come to be thought of in much the same light as the other scientific instrumentation spoken of—that is, as actual experimental devices, not only peripherally, in relation to other instrumentation, but by themselves. In this sense, a new kind of experimentation has begun in terms of the synthesis of computing elements into configurations that are capable of imitating important aspects of man's behavior and his physiological processes. The article on Analog Computers by Bellville and Hara in this issue serves as an informative and stimulating introduction to this new area of experimentation, stressing the engineering fundamentals of analog computers, pointing to the application of these principles in anesthesiology and medicine, in general, and comparing them, to a limited extent, with digital computers.

The general purpose digital computer is much spoken of and used (and, at times, *overused* or *misused*) these days, particularly in dealing with problems of all kinds that are reducible to complicated mathematical and statistical formulations. It has undoubtedly attained the position of pre-eminence in the computer field, whereas analog computers have come to be thought of in a much more specialized sense, as the tool of electrical engineers. Thus, one is identified with computation; the other, with engineering. In the article on analog computers the authors point out that the two types can often be regarded as interchangeable from the practical point of view. Nevertheless, there is the inescapable fact that the digital computer already requires literally no knowledge of the engineering aspects of the machine itself, whereas analog computers have not advanced to this point. Practically speaking, to use analog devices effectively and justifiably a certain minimum knowledge of electronics and electrical circuitry is a prerequisite. The first digital computers, of course, also required a certain amount of acquaintance with the engineering aspects. Programming was not so far removed from the internal workings of the machine; some knowledge of the machines themselves was necessary to compose a program for completely directing the electrical activities of the machine uninterruptedly toward its computational goal. However, the development of symbolic programming languages such as FORTRAN and ALGOL have made it possible to remain aloof from the machine itself and to deal entirely in terms of the mathematical functions of the machine, via a kind of algebraic symbolism and formalism—a machine symbolic language.

Another adjuvant to the general usefulness of the digital computer has been the mathematical field of Numerical Analysis, or numerical methods of approximation, which make it possible to render complicated mathematical expressions and functions in terms of the basic operation of addition, subtraction, multiplication and division. This branch of mathematics was previously implementable only on desk calculators and entailed sheer drudgery for the analyst; it required the utmost patience, care, and accuracy by the human operator, to say nothing of unlimited time. These factors seriously challenged the practicability of such mathematical procedures, and discouraged many mathematicians from even working in this field. The increasingly easy availability of digital computers, and of programming staffs supporting the larger facilities, makes it possible now to implement such procedures and to invent new complicated numerical procedures which can actually be carried out in practice in a reasonable time and with superhuman accuracy and precision.

The article by Bellville and Hara conveys the message that these same services are possible from analog computers. To prove the case, the basic engineering components and elements involved in the synthesis of such machines are explained and discussed in relation to the basic mathematical operations which are realizable in terms of such engineering hardware. The beginning point is the operational amplifier which forms the basic analog computer component. And it is clearly indicated how such units may be adapted to a variety of mathematical operations by the addition of other simple linear units such as resistors, condensers and potentiometers. Nonlinear multiplier elements are also discussed, as well as function generators and switching devices. In this way, it is also revealed, in some detail, that the analog computer performs its on-line data processing operations by sending input voltages through various electrical transformations designed to perform the electrical equivalents of mathematical operations.

Special purpose analog computers using these same principles may be built for solving particular problems, such as those involved in the analysis or monitoring of physiological signals. For example, if one is interested only in a display of the instantaneous rate of such a process, then a *differentiator* may be constructed which displays the derivatives of an input voltage curve appropriately scaled both in terms of time and amplitude. Thus, in addition to general purpose analog computers, it is possible to conceive of a special purpose device for each class of problem which, say, is widely studied in a laboratory or clinical environment.

Once a convenient mathematical representation or "mathematical model" of a given biological system is formulated, it may be programmed for a general purpose computer of either the analog or digital type, and by varying the conditions of the mathematical equations in terms of which the model may be expressed, we may then study the underlying process in a numerical sense by observing the effect on the computer output. Such studies are termed "simulation studies," or perhaps more descriptively, "*in numero*" studies, the latter term having been suggested by myself to connote that a new kind of numerical experimentation on biological systems is at hand which supplements the more classically thought of *in vitro* or *in vivo* experimental contexts. *In numero* studies attest to the basic importance of mathematical modeling as the bridge between biological problems and computer methodology, and of the computer in taking such models into the experimental domain. Extrapolations and inferences from data and artificial response curves generated in this fashion and comparisons with the results of actual responses obtained from biological systems may contribute toward a better understanding of the corresponding biological or medical system.

Analog computers may also be used in one other sense, briefly alluded to in the paper by Bellville and Hara. As an alternative to mathematical models, in some cases, electrical models or analogies of real or hypothesized biological or medical systems may be conceived quite directly which allow the system to be simulated by electrical circuitry, in effect. The realization of such electrical analogies in terms of the computing elements of analog computers allows, then, the synthesis of special analog computers which are capable of imitating important aspects of the behavior of the underlying system. Once such a machine is constructed the control constants or parameters may be manipulated in the form of knobs and dials until settings are found that produce reasonable fits to known outputs of particular systems. Many different kinds of physiological control processes may be studied in this manner and experimented on by projecting the system into the electrical domain. It is in fact possible to consider the construction of analog machines which may be utilized in a clinical therapeutic sense as control mechanisms, augmenting the natural system of control when indicated. This could be an aspect of the on-line utilization of analog computers, in cases where the analog computer can be demonstrated to be good enough to serve in a prosthetic sense.

There is, of course, always the danger that such analogies may be taken too literally. We should not assume that current engineering control theory even in the sophisticated form of a cybernetics is the final answer for biological control theory. Such an outgrowth of the engineering sciences does, however, provide us with an interim *ad hoc* language and theoretical framework with which to re-examine and recast our knowledge of biological processes. Nevertheless, it remains for biology and medicine to go on from there to something more specifically applicable to man. These problems are also being studied from the point of view of mathematical biology, and the combination of all such efforts may indeed produce a calculable rationale for dealing with and understanding the complicated problems of control in human systems.

Finally, it should be noted that from the point of view of medical education, at all levels, the new methodologies which are alluded to here and in the article by Bellville and Hara indicate areas in need of incorporation. Electrical principles, analog computer fundamentals such as those so well presented by them, and speaking even more generally and fundamentally, mathematics and physical science are the prerequisites for understanding developments along these lines that are sure to come.

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Functional Importance of the Hepatic Circulatory Changes Induced by Anesthesia

IN this issue of ANESTHESIOLOGY, Price and his co-authors, from the University of Pennsylvania and Columbia University, report their observations of the effects of halothane and cyclopropane on some aspects of the liver's metabolic activity. This work is important. For the first time, direct insight is provided into the possible significance of hepatic circulatory changes induced by general anesthetic agents.

It is well known that anesthesia may be accompanied by changes in hepatic perfusion.[1,2,3] The best evidence in man is that thiopental-nitrous oxide anesthesia by itself produces no change in the liver blood flow, while cyclopropane, halothane, and thiopental-nitrous oxide anesthesia complicated by carbon dioxide retention all reduce it. On the other hand, during halothane anesthesia, hypercapnia increases total perfusion, apparently because of the direct vasodilator effects of CO_2 together with the tendency of halothane to block sympathetic responses generally.

The present work now makes clear that these apparently similar (although differently mediated) effects on total hepatic perfusion are accompanied by differing metabolic actions with respect to the lactate-pyruvate system, which is important in the main chain of the conversion of glucose to energy. Cyclopropane produced a significant increase in "excess lactate"; halothane did not have this effect despite similar changes in blood flow. Furthermore, maneuvers which increase hepatic blood flow while maintaining anesthesia do not necessarily affect the metabolic changes seen in lactate and pyruvate metabolism. Nor was there evidence that changes in blood flow had any important effect on splanchnic oxygen utilization.

In the light of this study, and the preceding ones upon which it is based,[2,3] it now appears doubtful that hepatic circulatory changes of the magnitude described in normal subjects are responsible for significant effects on the integrity of hepatic function following uncomplicated anesthesia and operation, although they doubtless are of importance in determining the total circulatory adjustment to anesthesia. Furthermore, it is worth noting that hepatic dysfunction following anesthesia may be exaggerated by drugs or events which offset the hepatic circulatory effects, *e.g.*, hypercapnia during halothane anesthesia.[4]

One must recognize that hepatic blood flow may theoretically change in ways not completely reflected in measurements of total flow, and that such changes might well be of func-