The Application of New Knowledge to the Effective Administration of Anticancer Agents

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Summary

The evidence that some potent anticancer drugs are useful serves as a challenge to find out the basis for their selective action so that any general principles disclosed can be applied to devise more effective treatments. Despite much progress in identifying the locus of action of potent cytotoxic compounds, the basis for the chemotherapeutic action of any single anticancer drug cannot yet be stated with certainty. New physical technics are applicable to the direct measurement of the persistence of drugs in normal tissues and tumors. Better definition of the pharmacodynamic characteristics may be correlated with dosage regimens which can achieve better therapy. The dynamic interrelationship between the multiple physiologic and biochemical parameters, which determine the effect of a drug on one type of cell as opposed to another, cannot be analyzed in any simple manner. As sufficient data become available, the cellular parameters relevant to chemotherapy can be analyzed by computer simulation.

Physical Technics Applicable to the Study of Drug Metabolism

There is consensus on the need for the measurement of the blood levels of drugs as an essential part of any initial clinical investigation. The practical problem, however, is that accurate sensitive methods are available for only a few drugs. Satisfactory colorimetric or fluorometric procedures depend upon particular molecular properties and are not of general application. Suitably labeled radioactive compounds can be very useful if the molecule can be synthesized. Additional controls and careful interpretation are necessary, however, to correlate radioactivity measurements with the compound administered and its metabolic products. The use of new drugs requires the development of various analytic procedures most suitable for the needed study of physiologic disposition. The laboratory in which the need for such methodology arises is often not able to develop the procedures required because of inadequacies of personnel and instrumentation.

Without attempting to list examples which could be cited, it is appropriate to introduce into the brief discussion of this topic some awareness of the remarkable development of physical technics applicable to the measurement of minute amounts of drugs and metabolites. These procedures are based on the development of ingenious instrumentation which require skilled, experienced personnel. Such technics do not necessarily substitute for other analytic procedures if these are adequate, but they do allow analysis of drugs which are not measurable as satisfactorily by other means.

There is already a vast literature dealing with the physical technics applied to analysis of organic compounds and biologic materials. As one example, gas chromatography has been particularly useful in the analysis of lipids. There are many applications of gas-liquid chromatography in the field of toxicology and drug metabolism (1). Mass spectrometry can establish with certainty the fragmentation pattern characteristic of individual molecular species. The usefulness of this technic in establishing unequivocally the structure of organic compounds, on the basis of minute samples, can be applied to the identification of drugs and metabolic products in extracts of blood and tissues. A very powerful analytic tool results from the integrated system of coupling a gas-liquid chromatograph to a mass spectrometer. As one example, this technic made possible the determination of chlorpromazine in serum in nanogram amounts (3). Nuclear magnetic resonance spectroscopy can indicate the nature of the binding of small molecules to biopolymers. This technic is being used to study the structure and binding sites of enzymes (2) and for the measurement of enzyme kinetics (4).

Computer Methodology

Computer programming can simulate various models of biologic systems. The field of compartmental analysis has useful application to the kinetics of drug distribution and excretion. By programming a computer to simulate intestinal absorption, tissue distribution, and urinary excretion of an antibiotic, several possible models were eliminated as being incompatible with the experimental data (4). Thus, those parameters which best fit the data can be evaluated.

Sufficient information is available concerning Methotrexate to allow construction of a mathematical model of those cellular parameters relevant to chemotherapy (6). The parameters necessary to describe such a model include the rate of cellular uptake of Methotrexate and the rate of its excretion; the rate of synthesis of dihydrofolate reductase and the rate of breakdown of the free and Methotrexate-bound forms of this enzyme; the $K_m$ and $V_{max}$ of dihydrofolate reductase and of thymidylate synthetase; the cellular content of dihydrofolate reductase and tetrahydrofolate; the critical tetrahydrofolate concentration for thymidylate synthetase; the cell generation time and the duration of the S phase. The equations describing this model were translated into suitable
digital simulation language. Following hypothetical administration of different doses of Methotrexate, the behavior of the model tissue is indicated by the curves traced by the output plotter connected to the computer which show the levels of free drug, free reductase enzyme, and tetrahydrofolate cofactors, as well as the cell count, each in relation to time.

The validity of this model is shown by the evidence that it reproduces the well-known difference between the single dose and the multiple dose toxicity of Methotrexate. The total dose for the 50 percent lethality of a single injection of Methotrexate is some 70 times the total of divided daily doses. Thus, the behavior of this "electronic mouse" is satisfactory even though it is made up of an idealized tissue. To construct an electronic mouse bearing a tumor requires development of a more complex model, but this is feasible.

When a threefold difference in permeability of the drug was introduced, Dr. Werkheiser observed a point of particular interest in the behavior of the model. The "low permeability" tissue is more sensitive to large single doses of Methotrexate while the "high permeability" tissue is more sensitive to small repeated doses. Thus, data from the computer model lead to predictions of behavior to be tested by further comparative experiments with animals. By construction of an adequate model, the need for additional data is defined so that the necessary parameters can be accurately described.

Concluding Comments

Since whatever useful effects result from treatment with anticancer drugs available at present seem to depend upon quantitative differences in metabolism, it is imperative to amplify any such differences between host and neoplastic cells. Some real increases in therapeutic benefit have resulted from changes in dosage regimen. Yet, to determine an optimum dosage schedule for single treatments and combinations of drugs by suitable clinical trials is not feasible. The methodology can be developed to obtain data on the persistence of drugs in tumor and normal tissues. The parameters for the construction of computer models can be defined so that characteristics of drug behavior can be related to chemotherapeutic response. Such models have potential for the prediction of optimal dosage regimens. This certainly is a major task. Progress toward this objective requires close collaboration between clinicians and specialists in several aspects of pharmacology, in order to develop the data needed concerning those drugs selected for evaluation. A constructive step fundamental to such progress in cancer chemotherapy would be the establishment of several major centers providing the modern expensive instrumentation for the physical analytic technics and the development of methodology to study drug metabolism.

REFERENCES

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