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New Problems for Surgery

Drugs that act on the cell nucleus affect the surgeon's work on cancer and on transplantation.

Francis D. Moore

Iselin, in his Newcomen Lecture "The Pathfinder of the Seas" (*1*), said:

. . . no matter how pure the idealists among us try to keep science, there is little doubt that important advances frequently are achieved because someone realizes the practical applications that can be made of a particular course of study.

In biology, significant practical applications usually precede the completion of that "particular course of study" destined to elucidate the precise chemical or physiological mechanisms involved. The precise manner in which the digitalis leaf alters the irritability of the heart remains obscure despite 200 years of practice with clinical digitalization. A century of experience with ether anesthesia has failed to reveal to us the biochemistry of its action. Insulin therapy was used for 40 years before there was any satisfactory knowledge about its chemical structure or action. Today we are exploring the practical usefulness of drugs which affect the synthetic and mitotic activities of the cell nucleus. Although their practical usefulness is established beyond a doubt, it will increase as precise chemical and biological mechanisms are elucidated. Only then can the clinical investigator take advantage of the growing biochemical sophistication of his laboratory colleague.

It is no coincidence that the drugs used to treat cancer likewise interfere with the production of antibodies against transplanted tissues. But it is somewhat of a coincidence that the majority of patients who are treated with these drugs are under the care of surgeons. A hundred years ago the care of epithelial cancers (such as those of the esophagus, stomach, lung, rectum, bladder, kidney, breast, and thyroid) was shared by all doctors alike. There was very little compartmentalization or professional division. Indeed, very little could be done for the patient except to recognize the tumor and then to provide the simplest type of symptomatic treatment, analgesia, and compassion. This diffuse responsibility for the care of cancer changed to one of sharp focus by the rapid development of the techniques of sterile anesthetized tissue dissection, with blood transfusion and antibiotics, as a means for the total removal and thus the early cure of many malignant tumors. These events of the last 75 years have placed responsibility for the primary care of most cancers in adults squarely on the shoulders of the surgeon. He sees the patient first. If the tumor is early, he is the only person who has the golden opportunity to cure it—by removing it completely. In cases where that cannot be achieved, it remains the surgeon's responsibility to care for the patient through the long illness of recurrent and fatal malignancy. It is up to him to supervise or arrange for the other modalities of treatment, chiefly irradiation and chemotherapy.

In the field of tissue transplantation, responsibility is much more divided. Right from the start the surgeon shares his load with the physician who is expert in the management of the disease being treated by transplantation. Up to this time approximately 250 kidney transplantations have been done throughout the world; the kidney transplant, therefore, provides the model for this discussion, but the principles apply equally well to other tissues or organs. In the case of the kidney, it is the physician experienced in the study and care of patients with renal failure, renal hypertension, renal vascular disease, and degenerative cardiovascular processes who sees the patient first and helps to guide the surgeon in the preparation of the patient for operation and to assist in the management of the study and care of the patient during and after the operation.

For 75 years surgery has expanded by increasing the number of anatomical areas to which it can be successfully applied: the gut, the brain, the lungs,

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the heart. The use of the new chemical agents has brought new responsibilities to the surgeon fully analogous to those imposed by a new area of dissection. It is the purpose of this article briefly to review some of the new problems.

Cancer Chemotherapy

In 1948 Farber and his colleagues first reported the effects of aminopterin on acute leukemia in childhood (*2*). This opened possibilities in the treatment of advanced malignancy previously reserved only for a small group of late tumors amenable to whole-body irradiation. By the use of aminopterin and the many other cytotoxic agents that were soon to follow, treatment could now be offered to the patient dying of hopelessly widespread disease. Such treatment was offered, for the first time, with the announced hope of slowing the growth of a widespread tumor, or possibly even producing its regression, by means of a pill or an injection.

In epithelial cancers of the adult, the best results achieved to date have been short periods of stability or regression of the tumors. In the mesenchymal tumors of the blood-forming organs, such as the lymphomas and leukemias, and in certain other tumors of childhood (Wilms's, rhabdomyosarcoma), the benefits to be attained from drug therapy are much more impressive. These include long-term remissions and some that might even be termed cures.

It is in the epithelial tumors of adult life that the most pressing problems present themselves in the current study and use of cytotoxic drugs. These problems fall under the headings of (i) clinical investigation, (ii) host resistance, and (iii) treatment policies in late cancer.

As to *clinical investigation*: It is impressive to anyone who has treated a large number of patients with cancer chemotherapy that intelligent clinical research is very difficult to achieve. It is extremely unusual for the clinician to attain the clarity of result achieved by his laboratory colleague from whose chemical bench the drug originated. Even in the most conscientious hands the study of these drugs has often degenerated into bottle-off-the-shelf research—"let's try some of this new drug for a while."

Impressive difficulties in research in cancer chemotherapy are traceable, first, to the self-limited nature of the disease. There is rarely an opportunity to give a conscientious trial to more than one drug in a single patient because the generality of relief has been rare. Results can usually be gauged only by small differences between groups of patients whose comparability is often open to question. Other modalities of treatment must be used if the patients' interests are best served. These cloud the result.

Second, there are few discriminating chemical indices that can be used to gauge the progress of treatment—as tests for blood sugar, for example, gauge the effects of insulins. Such discriminating chemical indices might indicate growth or nongrowth of the tumor in a few days. As it is now, we know nothing of the result of a drug until many weeks have passed. An early favorable response, which might be revealed by a chemical change, is often masked completely by some supervening anatomical accident such as a pathological fracture.

One can name only a handful of chemical criteria for the short-term evaluation of drug action in cancer. These include measurement of the alkaline phosphatase in liver metastases, the acid phosphatase in prostatic carcinoma, the lactic dehydrogenase in a few widespread tumors, urinary calcium in skeletal involvement, and the excretory products of a relatively few secreting tumors: gonadotropins in choriocarcinoma, pressor amines in pheochromocytoma, corticosteroids in adrenal carcinoma, and indoleacetic acid in carcinoid. Beyond these few measures, we have nothing to rely on except weeks or months of clinical observation: the patient is better or worse, alive or dead.

General frustration with these two difficulties has led to national organization. One of the forms this takes is a sponsored national study in which the activities of many previously independent investigators are presided over by a corresponding secretary and formalized into a protocol, which is then to be employed throughout many hospitals. The drawbacks of this scheme have been that the protocol is likely to be prematurely crystallized on the basis of the concepts which went into the design of the study in the first place, so that the study becomes inflexible and unrewarding. Freedom to experiment with new combinations of drugs or radiation is discouraged in the participating hospitals. One of the least defensible of these national protocols is that which has dictated the use of a drug for a few days at the time of the primary operation. As one critic quipped, "An ineffective drug is being used for an inadequate time so that the results can be assessed by computer-programmed mathematics."

Increasing awareness of these difficulties has led to marked improvement in the past year. Newly formed groups are smaller, and the big, unwieldy ones have been reorganized. There are more frequent meetings to interchange ideas and results. There is greater flexibility and a much more sophisticated approach to clinical trials on an inter-hospital basis.

A national protocol was not necessary to show that ligation of the patent ductus arteriosus actually closes the shunt. A thousand patients were not needed to show that the subcutaneous implantation of pellets of deoxycorticosterone acetate was effective in producing salt retention. With increasing experience, group research will always leave room for this type of brilliant observation.

The effect of cancer chemotherapy on *host resistance* to the tumor has been given new meaning by the immunologic data emerging in the last 5 years from the laboratories of tissue transplantation. Tumor transplants have often been used as a model. The "take" of such tumor grafts is favored by the use of immunosuppressive chemotherapy with the very same cytotoxic agents that are used to treat cancer. The distinct possibility therefore arises that by the same agent we may be dampening some mitotic activity in the tumor while at the same time lowering the patient's resistance to the tumor. Thus it comes about that the two actions of these drugs are exhibited simultaneously in the cancer patient. Some of the baffling phenomena seen in treated patients who seem one day to be much better, and another week far worse, may be explained by this ambivalence of action: inhibiting mitotic activity and antibody synthesis simultaneously.

To study this double action, the investigator needs, not only the chemical indices of tumor growth previously mentioned, but also better methods for the measurement of the concentration of a drug in the blood and its excre-

tion in the urine, and for immunologic studies in cancer. Even the simplest of clinical reports should always include mention of those cases that appear to show an increased rate of tumor growth, as well as the usual categories of "no improvement" and "better."

Finally, as to *treatment policy* in the patient with late cancer: Such problems first arise when the patient first learns that he has a recurrent tumor. The tendency to "shop around" among institutions, seeking the "latest treatment," has been abated by the use of chemotherapy. Many patients have retained confidence in their institutions and in their doctors because chemotherapy was available to them in their extremity.

The cytotoxic agents have saved thousands of patients from being subjected to multiple small doses of creatine. With chemotherapy, the patient achieves the belief that something newly discovered is being used to help him. He believes that relief might be forthcoming, and in some cases it actually is. Therefore, so long as the drugs are used in doses which avoid systemic toxicity, the early use of these drugs during a recurrent phase of malignancy is justified on both psychological and medical grounds and is strongly urged even if the patient is asymptomatic.

The problems of treatment policy become much more difficult when the patient gets sicker. The drug must then be used in toxic concentrations or not at all. Bone-marrow depression, susceptibility to infection, and massive gastrointestinal hemorrhage are the three important complications from the use of these drugs. All three are likewise manifestations of the growth of cancer itself. It is often hard to tell which is at fault. Late cases are certainly not a good arena for the evaluation of drugs. But nonetheless the drugs must be used.

There is a current popular notion that doctors are too meddlesome in treating late cancer. Several members of the clergy have taken up the microphone, or the pen, to create a public image of the meddlesome doctor who prevents the patient from dying with what is hopefully referred to as "dignity." The patient is pictured as succumbing finally in a tangle of tracheotomy tubes, positive-pressure breathing apparatus, intravenous infusions, blood transfusions, and cancer chemotherapy. A decade ago such criticism would have been leveled at "ill-advised" colostomy, gastrostomy, or cordotomy. The "desperate" use of cancer chemotherapy, in the last decade, has taken the place of "meddlesome" surgical procedures as the butt of general criticism.

It is my conviction that the actual facts of medical treatment in late malignancy are far removed from this dismal image. In most hospitals, and in the hands of sophisticated surgeons and physicians, therapy in widespread cancer is neither meddlesome nor ill-advised. To an extent undreamed of by the laity, patients with advanced cancer can be rehabilitated by a variety of means. And, to an extent equally undreamed of by the general public, there is a considerate withholding of desperate treatment, usually with the knowledge of the family, and with watchful waiting and the use of analgesia in the last days of the patient. Actually, the withholding of such treatment demands as much discrimination as giving it. One must be certain, for example, that the "frozen pelvis" with ureteral obstruction is indeed due to cancer and not to radiation reaction, before advising that ureteral diversion be avoided and thus condemning the patient to a uremic death. Every consultant has seen patients to whom the withholding of treatment has brought much unnecessary misery.

In this setting of the last weeks of life it is indeed a challenge to the broadest type of clinical judgment, and the entire facility of a modern hospital, to use cancer chemotherapy intelligently. With all these precautions, there appears to be a final point in the progress of carcinoma of the colon, stomach, thyroid, breast, pancreas, and biliary tract beyond which the use of cancer chemotherapy rarely, if ever, yields a remission. At best it is only an emotional prop for the patient and his family, and at worst an immensely complicating factor, particularly through the production of massive gastrointestinal hemorrhage. It is the doctor's job to discern when this moment has arrived.

On a more optimistic note, the use of these drugs as continuous infusions or localized pump-oxygenator perfusions, their use with systemic antagonists, and their combined use with radiotherapy and surgery represent important new sources of hope for the patient with late malignancy, and they deserve intensive study.

Transplantation

Just 11 years after Farber's report on aminopterin, Schwartz and Dameshek reported the effect of 6-mercaptopurine on the production of antibodies against heterologous serum albumin in the New Zealand white rabbit (*3*). This report revolutionized an already rapidly evolving field. Like many other important discoveries in medicine and surgery, it was expected and indeed awaited. Within only a few weeks after its announcement, dogs at the Buxton-Browne Research Farm of the Royal College of Surgeons were under treatment by Calne with 6-mercaptopurine; prolonged acceptance of kidney transplants was soon reported, and within 8 months the first patient carrying a kidney transplant was on 6-mercaptopurine.

The subsequent chemical events in this field will not be reviewed here save to say that the synthesis of azathioprine by the group at the Burroughs-Wellcome Laboratories under G. H. Hitchings provided the drug which is used throughout the world today for immunosuppression. To these laboratories of a pharmaceutical corporation, many patients, and all physicians and surgeons working in this field, owe a debt of gratitude. There is little doubt that additional improvement in the chemistry of immunosuppressive drugs will be forthcoming in the near future.

It is my intent to review here certain problems of tissue transplantation, and kidney transplantation in particular, broadly organized as under (i) drug evaluation, (ii) donor selection, and (iii) policy for the beginner.

As to *drug evaluation*, the problem here is far simpler than in cancer chemotherapy. Concentrated and independent activity in several laboratories should be encouraged and financed on a broad scale. From the results already attained with 6-mercaptopurine, azathioprine, azaserine, actinomycin, and methotrexate, it is evident that we are dealing with a wide range of pharmacologic activity. There is a readily available animal model for this work, because it appears that the dog with a kidney transplant after bilateral nephrectomy offers a reasonable reflection of what is to be expected in man. This animal model has been used in many thousands of instances and has made it possible for kidney transplantation to move to the clinic. But it is a very expensive animal preparation, far

more so than one employing mice. Each dog must be suitably selected, subjected to the proper immunization against kennel diseases, and given pre- and postoperative care, which, while not truly that of a totally aseptic environment, must nonetheless be controlled. This includes multiple blood transfusions, multiple drugs, and antibiotics, with daily biochemical studies to assess the progress of the graft and the resistance of the host. All the care of a modern hospital is lavished on each dog. At the time the operation is completed and the biochemical course begun, an impressive sum has been invested in a single test animal. And the initial screening of a single compound requires at least 20 animals.

To rely completely upon kidney transplants in dogs for carrying out the drug evaluation that remains to be done would require more extensive laboratories than any now available. The work is of great importance and should be further supported within the capacities of our institutions to undertake it. But likewise it is important to develop a simpler animal screen. Such might be the heterologous blood-cell system in the mouse, or the injection of heterologous serum albumin in the rabbit as originally used by Schwartz and Dameshek. In both these models a small animal is presented with the antigenic stimulus of a component of blood from a different species. The immune response is very readily measured by radioactive tag on the antigen. In both models the response is suppressed by chemotherapy. Skin transplants would also be an appealing system for the study of chemotherapy were it not for the fact that they are quite difficult to maintain by means of immunosuppression, even though skin has been the research model for much of the immunologic study of homotransplant rejection.

Once a drug has shown its effectiveness in the laboratory as a means of diminishing antibody formation against transplanted tissue, then its clinical trial in man is far simpler than the study of cancer chemotherapy. The progress of the graft can be followed from day to day and even from hour to hour by standard chemical and radioisotope techniques. It is possible to titrate the action of the drug against the rejection potential of the patient. This whole subject is one that gives much promise of fruitful investigation and very rapid improvement in drug chemistry and clinical management.

It is the *selection of donors* that presents the chief dilemma in transplantation today. The living human donor provides by far the best tissue, and donors who are closely related to the patients appear to yield the highest incidence of successful long-term transplants. Thus, for the first time in the history of medicine a procedure is being adopted in which a perfectly healthy person is injured permanently in order to improve the well-being of another. Some laboratories have viewed this matter with such misgivings that under no circumstances have they used tissues from volunteer human donors, either related or unrelated; even the idea of using an identical twin as donor of a kidney has been viewed with suspicion.

The surgical department of which I am a member has taken quite the other view. It has been our conviction that with careful selection of a donor, with evaluation of bilateral renal function, with vascular anatomy ascertained by aortogram, and with proper precautions regarding blood-group compatibility, we can offer the patient the best results available, and that it is better to do this than to dodge the donor problem by relying wholly on cadaver kidneys, thereby offering the patient something second best. We have been fortunate in this regard. In our kidney transplantation program we have never lost a donor. But no matter how fine the record, one cannot deny the realities of present injury and future jeopardy.

Current efforts to improve the procurement and preservation of tissues from cadavers by post-mortem cooling and short-term tissue hypothermia are the most hopeful channels for solution of this problem. In unpaired organs such as the liver such steps are, of course, essential. The difficulties are enormous. In a recent survey of deaths in our hospital, we found that less than 10 percent of all the cadavers would be satisfactory as tissue donors. Advanced age, infection, malignancy, shock, vascular disease, all take their toll from the tissues or organs which might be used to help the living. When to this is added the necessity of blood-group compatibility, a waiting period of many weeks or months must ensue even in very large hospitals before the ideal donor comes along.

The possible use of animals as tissue donors would provide another solution. Heterotransplant research has occupied the attention of scholars since the early work of Carrel. Heterotransplants have usually been done between animals rather far removed in relationship: goat to dog, rat to rabbit. Recent reports of a chimpanzee donor for a human patient represent the conscientious result of careful work by competent investigators who have given much thought to heterotransplants between members of the primate order. The exact role of immunosuppressive chemotherapy here, and the possibility that immunosuppression of the type useful in homotransplants will also be effective in heterotransplants, have excited great interest in the workers in this field. Until further study has been accomplished on the fate of heterografts between primates, the choice between the rare cadaver and the readily available, living human donor will remain an important decision in kidney transplantation.

Finally, as to *policy for beginners* in transplantation: Dozens of hospitals and laboratories in this country and abroad are preparing to enter this field, and applications are under consideration by the National Institutes of Health for large sums to finance new ventures in transplantation. Because transplantation offers hope of life in illnesses hitherto fatal, this widespread interest must be encouraged. It is not clear, however, that the interest and the preparations are always accompanied by an adequate appreciation of the difficulties to be overcome. The development of clinical transplantation in this country has reached its present stage largely as the result of activities in three or four laboratories which have been working in the field for almost two decades. In these institutions and in the hands of these doctors, the many challenging facets of the problems are appreciated if not solved, and much experience has been gained in managing them. These facets include the continuing care of the patient with renal failure by multiple extracorporeal or peritoneal dialysis, the problems of donor selection already mentioned, vascular anastomosis, prevention of infection, identification and treatment of the postoperative immunologic-rejection crisis, and adjustment of the dose of immunosuppressive drugs, with or without radiotherapy and splenectomy. With compatible family donors, current short-term success-rates (survival over 6 months) run from 75 to 80

percent, a figure unattainable 2 years ago.

In the transplantation of kidneys, four essential disciplines are involved: renal physiology, vascular anastomosis, urologic management, and immunosuppressive chemotherapy. Yet our laboratories are sought out each year by visitors who wish to spend 2 to 3 days with us so that they may then return home and take over the transplant problems in their own hospitals. Usually these are individuals who are familiar with only one of the four disciplines involved and often devoid of teammates to assist them.

An urgent problem therefore arises concerning what sort of regulation should be undertaken in such a field. The "free enterprise" system which is so characteristic of our country in medicine and surgery shows itself at its very weakest when such a development as this suddenly explodes into clinical application.

An analogy with the development of open-heart surgery suggests itself, but there is an important difference. Open-heart surgery for the repair of congenital or acquired defects became available 10 years ago as the result of work in three or four laboratories. Many hospitals then wished to enter the field. But in the case of open-heart operations there was a wonderfully effective deterrent to irresponsible application: the procedure itself. No one in his wildest dreams would undertake the extracorporeal pump oxygenation and total body perfusion of a fully anesthetized patient in late congestive heart failure, with thoractomy and cardiotomy of the left ventricle, without first carrying out an extensive series of experiments in the laboratory to assure his competence in such simple matters as the maintenance of proper circulation and normal blood chemistry. In short, the pump oxygenator itself was a sufficiently complicated and fearsome device to constitute a deterrent to irresponsible adventure.

Unfortunately, kidney transplantation has no such built-in deterrent. It looks deceptively easy. Even though mortality and morbidity are still impressive, anyone who is caring for a patient with renal failure and who is competent to join two blood vessels together with fine sutures may feel entitled to undertake the operation. But he should be discouraged unless he has taken pains to assure his own knowledgeability and competence in the field. Any surgeon who wishes to transplant kidneys in people should take at least a year off from his ordinary activities to set up a laboratory enterprise in which the entire procedure can be performed repeatedly in experimental animals and with accurate biochemical control. The members of the four-man team should spend, not days, but several months working together in the laboratory on this problem. The responsibility of surgeons and of organized medicine is here very grave indeed. A new therapeutic device of remarkable effectiveness, awaited for centuries, has finally arrived because of the development of chemical compounds that suppress the formation of antibodies. The chemistry is complex; the simplicity of the surgery should not blind us to the hazards.

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News and Comment

NIH: Budget Hits $1-Billion Mark for First Time, But No One Seems To Be in a Mood for Celebration

The National Institutes of Health was certified for the billion-dollar-a-year rank this month, a milestone that might normally evoke a speech, or at least a cheer or two, especially if it's recalled that just one decade back the budget was $81 million.

But this is clearly a time of doldrums on the scientific-financial scene, a condition that was reflected by the hearings and report recently released by the House Appropriations subcommittee which reviews the NIH budget.*

The subcommittee, in reporting out $1.045 billion for NIH, a $70-million increase over the current budget, accurately noted that NIH's budgetary growth had tapered off sharply, and it described the budget as "disappointing," "unduly mechanical," and "one of the most conservative . . . submitted to Congress in recent years."

Nevertheless, the subcommittee, for the second straight year, refrained from its previous practice of piling funds on top of the amount requested by the administration. Its decision clearly reflects a judgment that neither the executive nor the congress is in a mood, for the present, at least, to resume the fast growth that characterized research and development expenditures through the 1950's and the first two years of this decade. Conceivably, something might have been tacked on to the budget and steered through Congress, but the executive branch can't be made to spend what it doesn't want to spend. And in this election year, the Johnson Administration has made it clear that it isn't fooling about keeping down the federal budget.

As a result, the subcommittee took the administration's request of $1.049 billion, cut out a perfunctory $4 million, and let it be known that though it was very unhappy about NIH not getting more, it wasn't going to try to do anything about it. For the subcommittee to have cut anything at all if it felt the overall total was inadequate may seem contradictory, but in a billion-dollar budget, $4 million can be easily absorbed, and in a conservative congress a little pruning looks good, even if it is financially insignificant.

Throughout the hearings, which, by House custom, were held behind closed doors, subcommittee chairman, John

* "Hearings on Department of Labor and Health, Education and Welfare Appropriations for 1965," parts 2 and 3, and "Committee Report," available without charge from Appropriations Committee, U.S. House of Representatives, Washington, D.C.