Washington 98104, USA), solar powered refrigeration,[5] and the silver swaddler,[6] which is used to transfer low birthweight babies to a neonatal unit. At the same time, several traditional techniques—for example, acupuncture and an upright position during childbirth—are being evaluated scientifically, so perhaps the transfer of technology ought not to be considered as a one way process.

Some critically annotated lists of best buys among health related appropriate technologies could provide tremendous support for primary health care movements in all countries and enable those concerned to use their limited resources wisely. In addition, this information may help voluntary agencies and charitable organisations to function more effectively and avoid inappropriate equipment in areas where technical help is urgently needed. These challenges must not be overlooked at a time when so much attention is given to the continuing advance of the frontiers of medical research.

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Acquired resistance to cancer chemotherapy

Many human cancers, such as colorectal carcinoma or malignant melanoma, are naturally resistant to anticancer drugs, and the results of treatment are poor. Other tumours, however, may respond well to drugs at first, but eventually the treatment fails because the cancer becomes drug resistant. For example, patients with breast cancer or advanced small cell cancer of the lung commonly improve with chemotherapy, but eventual treatment failure is almost invariable. Even among tumours which can be cured by chemotherapy, such as Hodgkin's disease, testicular cancer, or acute leukaemia, acquired resistance leads to failure in a quarter to a half of cases. What, then, do we know of the mechanisms of acquired resistance, and how may it be overcome?

Among the factors determining the outcome of cancer chemotherapy are the patient's ability to absorb or activate drugs, the tolerance of normal tissues, the penetration of drugs into the sites of disease in the body, and their ability to penetrate the tumours themselves—which may be poorly vascularised. The drug must cross the cell membrane; and the final outcome will then depend on the biochemical make up of the cell—and, to some extent, on its proliferative state.

Clinical failure of treatment after an initial response may result from changes in any of these factors. Normal tissue tolerance is a common practical limitation. Sanctuary sites where drugs cannot penetrate may lead to relapse: the central nervous system is such a site in acute leukaemia. Poor tumour vascularity has been shown to limit the effectiveness of treatment in laboratory studies,[1] but whether in a clinical setting changes in vascularity can lead to a newly acquired resistance after initial sensitivity is not yet known. Some phases of the proliferative cycle of a cell are known to be relatively resistant to some drugs,[2] but there is little evidence that human tumours which are initially sensitive to a drug become resistant by altering their proliferation kinetics.

Commonly, acquired resistance seems to be due to biochemical changes within the tumour cells. The differences between sensitive and resistant cells have been defined in detail for a number of experimental systems. Tumour cells have been exposed to a drug in vitro or in vivo until resistance has become apparent and the biochemical make up of the resistant variant compared with the "wild" tumour cell. Results obtained in this way need to be assessed with caution, for the circumstances are very different from those found in clinical practice. Such research does, however, provide valuable insights into potential mechanisms.

One of the best understood examples is the antimetabolite methotrexate. This drug enters cells by an energy dependent process and inhibits dihydrofolate reductase, a key enzyme in folate metabolism, which is necessary for the synthesis of nucleic acid precursors. When human and murine tumours are exposed to continuous low concentrations or graded increases in the concentration of methotrexate in vitro they become resistant for several well defined different reasons.[3 4] Uptake of the drug into cells may be reduced, mutant enzymes with a low affinity for the drug may be synthesised, or the amount of dihydrofolate reductase enzyme within the cell may be increased. In resistant cells which contain excess dihydrofolate reductase the gene which codes for this enzyme is present in greatly increased number. These amplified genes can exist either as an integrated part of a cellular chromosome (identified as a homogeneously staining region on karyotypic analysis) or as separate small pieces of DNA, so called "double minute" chromosomes. Since double minute chromosomes do not segregate and may be lost during cell division, resistance to methotrexate may be unstable when the selection pressure in favour of resistant cells is removed.[5 6]

The cellular basis of experimentally induced drug resistance is now known (at least in part) for many other anticancer drugs. Mechanisms include failure of drug uptake or activation, increased drug efflux or catabolism, mutant target enzymes, or increased repair of damage to DNA.[7 8] The patterns of cross resistance or sensitivity have been worked out in detail for murine tumours.[9] Much interest has been focused recently on alterations in the cell membrane which appear to induce resistance to several drugs of different groups—so called pleomorphic drug resistance.[10] Some of these many mechanisms probably do underlie clinical drug resistance, but much work remains to be done to clarify their relevance to clinical practice.

Exactly how cells with a drug resistance phenotype come to dominate the tumour is not yet entirely clear. The early work of Luria and Delbruck on the resistance of bacteria to bacteriophage provided an important experimental model in which acquired resistance was due to the selection by the bacteriophage of spontaneously occurring mutations.[11] Studies applying the same methods to mammalian neoplastic cells have suggested that a similar process of mutation selection occurs when cancer cells are treated with drugs.[12 13] Goldie and Coldman developed a mathematical model of this process.[14]

If cell mutation is random then for any given mutation rate the probability of a tumour containing a single drug resistant cell increases with the size of the tumour. Their model predicts that the probability of a resistant mutation increases quickly during quite a short part of a tumour's early life and that this leads to clinical incurability. Clinical experience would certainly support the suggestion that larger tumours are harder to cure than smaller ones, but there may be many reasons for this.

The mutation selection model provides a useful framework for research into drug resistance, but it is clearly not the whole story. In some circumstances cells may phenotypically adapt to resist a cytotoxic agent such as a monoclonal antibody. Many anticancer drugs are potent mutagens and may directly induce resistant mutants. Tumour cells may interact (both in vivo and in vitro), and these interactions may influence drug sensitivity.[15] Genetic information can be transferred between mammalian cells by a variety of methods in vitro, and conceivably resistance might be transferred by a process analogous to transfer of antibiotic resistance between bacteria.

The new techniques of molecular biology are now being applied to the problem of resistance to anticancer treatments. Resistance to the cytotoxic effect of ultraviolet light and to drugs has been conferred on sensitive mammalian cells by the transfer of DNA from resistant cells.[16] These new methods provide powerful tools for the analysis of the genetic basis of drug resistance.

Cells from the bone marrow and the gastrointestinal tract, which are the normal tissues most often critically affected by cancer chemotherapy, do not seem to acquire drug resistance. The biological basis of this difference is unknown but may lie in their cell renewal systems, in which the stem cells appear to be dividing slowly and perhaps undergo spontaneous mutation infrequently. Normal murine marrow cells, however, treated in vitro with DNA from methotrexate resistant cell lines, can be transplanted into mice which are then rendered resistant to this drug.[17 18] These remarkable experiments present the possibility of selective modification of cellular drug resistance by molecular genetic techniques which may have important implications for biology and medicine.

As yet methods for overcoming or avoiding the acquisition of drug resistance have met limited success, but several interesting lines of inquiry are being pursued.[7] The use of drug combinations and intermittent schedules of administration may avoid or reduce the development of resistance. Progressive rises in the dose of a drug are usually limited by normal tissue tolerance, but high doses of alkylating agents appear to be effective in some apparently resistant tumours.[19] As our understanding of specific biochemical resistance mechanisms is improved more useful therapeutic ideas should emerge. For example, if resistance is due to increased quantities of the target enzyme—as with dihydrofolate reductase and methotrexate—new agents might be designed which are activated by that enzyme. Goldie and Coldman have suggested that the development of resistance may be best avoided by the early use of alternating drug combinations which may not induce cross resistance, and early clinical experience seems to support this view.[20]

We know a great deal about acquired drug resistance but we still have a great deal to learn. Further work will define the biochemical mechanisms of resistance which actually operate in human cancer rather than in experimental models and the part to be played by the techniques of molecular biology for investigation and perhaps therapeutic manipulation.

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