Papers and Originals

Cancer Chemotherapy—The First Twenty-five Years*

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My aim in this lecture is to review and comment on the progress of cancer chemotherapy during the past 25 years. It is customary when using this term to exclude treatment of malignant disease with hormones, and though not subscribing to its logic, I propose to observe this convention.

This branch of therapeutics cannot be said to have enjoyed an orderly growth. The very notion expressed by the phrase "cancer chemotherapy" would have been incomprehensible a quarter of a century ago. Indeed, the claim that malignant disease could be controlled and might even be cured by drugs would have been considered more appropriate to the charlatan than to the physician. His place was but to administer the medical equivalent of extreme unction—opiates and comfortable words. During these years there has been a complete change in attitude. That drugs may influence tumour growth is accepted as a self-evident fact, and this acceptance itself has stimulated inquiry into the possible antineoplastic properties of innumerable previously neglected natural and synthetic products.

Before 1945 cancer chemotherapy existed no more in fact than it did in name. Its development since that year may be viewed from several standpoints. The chemist, the pharmacologist, and the experimental chemotherapist have made immeasurable contributions to the subject and their perspectives would doubtless differ from that of the practising physician, which is necessarily mine. He is forced by his circumstances to take a bleakly pragmatic view and to confine his interest largely to the tangible successes that cancer chemotherapy has achieved. Its growth in the past 25 years has been luxuriant but incoherent. Unrelated chance observations have served as starting points for massive research projects. Vast numbers of agents, some naturally occurring, some synthetic, often selected at random, have been subjected to a process of screening for antineoplastic properties. For the clinician, however, the story of cancer chemotherapy is the story of the drugs which have proved to possess therapeutic activity.

From the historical point of view these drugs fall into three groups—alkylating agents, the antimetabolites, and a miscellaneous assortment containing various plant derivatives, antibiotics, and agents initially synthesized for other purposes. The first alkylating agent to be used in medicine was mustine hydrochloride, familiar as nitrogen mustard or HN_2. During the first world war leucopenia had been noted in those dying from exposure to mustard gas (Stewart, 1918; Krumbhaar, 1919), and in 1940 its nitrogen derivative, prepared for use in chemical warfare, was found to have like effects. A possible therapeutic use in leukaemia occurred to workers on both sides of the Atlantic, and satisfactory results in the treatment of this and other disorders were reported. The publication of these observations in 1946 and 1947 was the seminal event in the development of cancer chemotherapy (Gilman and Philips, 1946; Goodman *et al.*, 1946; Rhoads, 1946; Wilkinson and Fletcher, 1947).

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Alkylating Agents

It was rapidly appreciated that the biological action of mustine was due to its power of alkylation—that is, to the ability of its alkyl radicals to combine with susceptible groups in the tissues. Moreover, since it possessed two reactive alkyl radicals, each molecule was capable of combining with two such groups. Mustine required intravenous injection, was irritant to the tissues and unstable in solution; to overcome these disadvantages many other alkylating agents were submitted to clinical trial. They included derivatives of mustine in which various prosthetic groups were substituted for its methyl radical, as well as unrelated agents such as the dimethane sulphonates. Mustine is converted in solution to an ethyleneimmonium ion which is the effective alkylating agency. This suggested that polyethyleneimine compounds might have similar therapeutic effects, and trials with triethylenemelamine and with the diepoxides, both of which had been in use for many years in the textile industry, proved this true.

These compounds owe their antineoplastic activity to possessing two reactive alkyl groups. Agents with only one have but 1–2% of the potency of the bifunctional preparations. They exert their effects by alkylation of deoxyribonucleic acid (DNA). The point at which this reaction takes place is at the nitrogen atom in the 7-position on the imidazole ring of the purine base guanine. The two alkyl groups link together opposed guanine molecules on the two strands of DNA where a twist in the helix approximates them, preventing the helix uncoiling and arresting replication of DNA. This explains not only the importance of bifunctionality but also the observation that there is an optimum distance between the reactive groups above and below which activity falls off rapidly (Ross, 1962; Boesen and Davis, 1969).

It seems probable that the ultimate effects of alkylation are similar for all the preparations under discussion. Though each drug may have additional actions which are difficult to explain, all possess the capacity to damage bone marrow and to suppress the immunity mechanisms.

Alkylating agents which have been synthesized and screened outnumber the sands of the sea, but those which have won a place in practical therapeutics are few. They fall into four groups: the nitrogen mustards, the ethyleneimmonium compounds, the sulphonic acid esters, and the diepoxides.

Nitrogen Mustards

Mustine Hydrochloride.—Only four nitrogen mustards have firmly established themselves. Mustine hydrochloride, the great progenitor of them all, retains its place because of its rapidity of action. Its main value is in Hodgkin's disease and lymphosarcoma.

Chlorambucil, a phenylbutyric acid mustard, was synthesized in the hope that advantage would accrue from its increased solubility (Everett, *et al.*, 1953). It has a direct destructive action on circulating lymphocytes as well as on lymphoid tissue and is thus of particular value in chronic lymphatic leukaemia, lymphosarcoma, and Waldenström's

macroglobulinaemia. It is much used in Hodgkin's disease and has given good results in ovarian carcinoma and seminoma (Galton *et al.*, 1961; Boesen *et al.*, 1964; Wiltshaw, 1965).

Melphalan, a phenylalanine mustard, was designed on the assumption that the prosthetic amino-acid would lead to its incorporation in the cell's metabolic processes and so to its concentration within the tumour. It was synthesized almost simultaneously in this country and the Soviet Union (Bergel and Stock, 1953; Larionov *et al.*, 1955). In Great Britain the laevorotatory isomer was used; the Russian product, sarcolysin, was optically inactive and only half as potent as melphalan, owing to the dextrorotatory isomer being inert. The reason for this curious difference is unexplained. Its main value is in the treatment of myelomatosis, though it has some effect also in seminoma and is used as a perfusate in regional chemotherapy (Waldenström, 1964).

Cyclophosphamide is a cyclic phosphoramide mustard, and its history provides a salutary caution against the rigid application of logic to the development of cancer chemotherapy (Brock, 1957; Arnold *et al.*, 1958a, 1958b). The knowledge that tumours were richer in phosphoramidases than healthy tissues suggested that an agent which was inert until split by such enzymes would be selectively concentrated in active form in malignant cells. Cyclophosphamide is inactive in vitro and remains so in serum, but the attractive hypothesis which inspired its inventor was demolished by finding that incubation with tumour homogenates did not convert the drug to the active form, though the intact liver did. In spite of its insecure theoretical foundation, it has proved a useful drug. It is of great value in Hodgkin's disease, myelomatosis, chronic lymphatic leukaemia, and reticulosarcoma, and often of benefit in mammary and ovarian carcinoma (Coggins *et al.*, 1959; Haar *et al.*, 1960; Matthias *et al.*, 1960; Fairley and Simister, 1964). It leads to alopecia more readily than other alkylating agents, and irritant metabolites excreted in the urine are apt to produce a chemical cystitis. It has the advantage of being less myelotoxic than other nitrogen mustards.

Ethyleneimmonium Compounds

The ethyleneimmonium compounds are little used nowadays. Triethylenemelamine, bottles of which had long been gathering dust on the shelves of textile factories, was shown to have antineoplastic activity in animals (Philips and Thiersch, 1950), but its clinical use was invalidated by its variable absorption. Its successors were triethyleneiminothiophosphoramide, or thiotepa, and a benzoquinone derivative known as triaziquone (Trenimon), widely used in Germany but seldom in this country. *Thiotepa* is the only important member of this class. There are records of it giving occasional surprisingly good results, often with less common tumours such as fibrosarcoma and rhabdomyosarcoma; it has also proved effective in some patients with malignant melanoma and carcinoma of the breast and of the ovary (Shay *et al.*, 1953; Leonard *et al.*, 1956). In general it has no advantages over nitrogen mustards such as chlorambucil.

Dimethanesulphonates

During the heyday of the nitrogen mustards other alkylating agents which might have antineoplastic activity were eagerly sought. Among these a series of dimethanesulphonates was synthesized, of which the most active proved to be 1,4-dimethanesulphonoxybutane, or busulphan (Haddow and Timmis, 1951, 1953). The higher and lower members of the series are less effective, possibly because the two alkylating radicals are separated in busulphan by a distance critical for cross-linking of the opposed guanine bases in the DNA molecules. Busulphan has an almost selective effect on granulopoiesis (Elson, 1955). This property, which is unexplained, has made it the treatment of choice in chronic myeloid leukaemia, ousting radiotherapy from half a century of supremacy (Galton and Till, 1955; M.R.C., 1968). It has some value too in the other myeloproliferative syndromes.

Diepoxides

The final group of alkylating agents, the diepoxides, has been used little in this country. Like the polyethyleneimines they have been used in the textile industry, where their cross-linking properties prevent shrinking of wool. The earlier members, diepoxybutane and eponate, proved disappointing (Miller *et al.*, 1960), but a third, ethoglucid (triethyleneglycol diglycidyl ether), appears to hold more promise (Lees, 1965).

This brief review of the alkylating agents in common use shows that while they all possess myelotoxic properties their therapeutic actions differ inexplicably. It is, for instance, not clear why busulphan should be a near specific for chronic myeloid leukaemia, or why chlorambucil should be so valuable in macroglobulinaemia or melphalan in myelomatosis. It is perhaps wise to accept such claims of specificity with reserve. A clinician is apt to display uncritical affection for a drug, the value of which he has helped to establish; he comes to understand it, to use it with confidence and skill, and forsaking all other to keep only unto it. Once an agent has proved itself effective no one feels inclined to use a closely related drug, the action of which will almost certainly be similar and possibly less beneficial. It is reasonable to suspect that the alkylating agents have a more extensive common range of action than is proved. Nevertheless, they do present differences which it is hard to explain if their biological effects depend on alkylation alone.

Antimetabolites

The antimetabolites make up the second group. An antimetabolite exerts its effect by successful competition with the normal substrate of an enzyme system. It closely resembles the metabolite and thus engages with the enzyme, but because it is not identical with the normal substrate the reaction cannot proceed to completion and this particular metabolic pathway is blocked. Antimetabolites have been widely exploited in cancer chemotherapy, usually with the aim of impeding the synthesis of nucleic acids.

The first step in this development was empirical. When folic acid was isolated in 1946 (Angier *et al.*, 1946) its conjugates were prescribed widely and often uncritically. Farber believed that this drug accelerated the progress of acute leukaemia and reasoned that an antagonist might have the reverse effect. Later he published reports which proved the validity of his argument (Farber *et al.*, 1948). About this time the importance of nucleic acid biosynthesis was gaining recognition, and it was soon seen that the folic acid antagonists must interfere with the process. This in its turn led to the search for other metabolic antagonists likely to impede nucleic acid synthesis, and attention was focused on those directed against the formation of purines and pyrimidines, the raw materials of DNA.

Folic Acid Antagonists

In vivo folic acid is reduced enzymatically to tetrahydrofolic acid, which acts as a coenzyme in the process of "one-carbon transfer." Its most important action is the methylation of deoxyuridylic acid to form thymidylic acid. Methotrexate, the only one of these antagonists now in clinical use, has an affinity for folic acid reductase 100,000 times greater than that

of folic acid itself. Its action thus blocks the production of tetrahydrofolic acid, inhibiting the formation of thymidylic acid and consequently of DNA. Methotrexate is used most frequently in the maintenance treatment of acute lymphoblastic leukaemia (Farber *et al.*, 1956; Holland, 1961), but its greatest success has been in choriocarcinoma (Bagshawe, 1962, 1963; Hammond *et al.*, 1967). Injected intrathecally it has been of value in controlling the neurological complications of acute leukaemia (Hyman *et al.*, 1965). It has been given by intra-arterial perfusion in regional chemotherapy when the systemic toxic effects can be prevented by parenteral injection of folinic or 5-formyl-tetrahydrofolic acid, the metabolite production of which it blocks.

Purine Antagonists

A large number of purine analogues have been examined for antineoplastic properties, but the only two of clinical value are 6-mercaptopurine (Elion *et al.*, 1952) and 6-thioguanine (Philips *et al.*, 1954a, 1954b). Both are converted to their ribotides in vivo: the first acts at several different points in the early stages of de novo purine synthesis; the second is thought to be incorporated into DNA and the abnormal molecule thus formed is unable to use guanine.

Both are used in the treatment of acute leukaemia. 6-Mercaptopurine is more valuable in maintenance than induction of remission (Burchenal *et al.*, 1953). The place of 6-thioguanine is still uncertain. In combination with other drugs it has given a high remission rate in acute myeloblastic leukaemia (Gee *et al.*, 1969).

Pyrimidine Antagonists

Of the innumerable pyrimidine antagonists which have been synthesized and submitted to screening, only three have an established value. These are 5-fluorouracil, 6-azauracil, and cytosine arabinoside.

The two pyrimidine bases, thymine and cytosine, are synthesized from carbamyl-aspartic acid by way of orotodylic acid and the nucleotides uridylic, cytidylic, deoxycytidylic, and thymidylic acids.

5-Fluorouracil (Duchinsky *et al.*, 1957), the best-known pyrimidine antagonist, exerts its effect only after conversion to its deoxyribonucleotide, blocking the enzyme thymidylate synthetase and thus inhibiting the methylation of deoxyuridylic to thymidylic acid (Harbers *et al.*, 1959). Thus it acts at the same point in the metabolic pathway as methotrexate, but in a different fashion. 5-Fluorouracil has been widely studied, but its therapeutic value is small. It has some effect on carcinoma of the alimentary tract and breast, but its considerable toxicity limits its usefulness (Vaitkevicius *et al.*, 1961; Weiss *et al.*, 1961).

6-Azauracil has not been widely used because of its neurotoxic effects. After conversion to its deoxyribonucleotide it inhibits the decarboxylatin of orotodylic to uridylic acid (Prusoff *et al.*, 1956). Its riboside, 6-azauridine, is less toxic and has been found of some value in acute leukaemia (Welch, 1961).

Cytosine arabinoside (Bergmann and Feeney, 1951) interferes with the formation of deoxycytidylic acid from cytidylic acid and thus inhibits DNA synthesis. It becomes active only after phosphorylation. It is a valuable drug in the treatment of acute myeloblastic leukaemia, particularly when used in combination (Burchenal *et al.*, 1966; Howard *et al.*, 1966; Acute Leukaemia Cooperative Group B, 1968; Gee *et al.*, 1969; Crowther *et al.*, 1970).

Miscellaneous Antineoplastic Agents

The third group includes vegetable products, antibiotics, and a miscellany which cannot be classified. Their antineoplastic properties have usually been a chance discovery of random screening and in most the mode of action is unknown.

Vegetable Extracts

The three plant extracts with therapeutic value share the property of arresting mitosis in metaphase, though it is unlikely that this explains their antineoplastic activity, for their chemical structure and clinical applications all differ widely.

Colchicine, derived from the autumn crocus (*Colchicum autumnale*), was found to have an antimitotic action in 1934. Its toxicity made it unacceptable and it was replaced by deacetyl-N-methylcolchicine (demecolcine; Colcemid), rarely used now but of some benefit in chronic myeloid leukaemia (Sokal and Krauss, 1963) and Hodgkin's disease (Vercillo and Esposito, 1958).

Vinca Alkaloids.—The other two extracts come from the West Indian periwinkle (*Vinca rosea*). An infusion of its leaves had long enjoyed a local reputation as a cure for diabetes mellitus. It was found that over 30 alkaloids could be isolated from this plant; none caused hypoglycaemia but four had antineoplastic properties, though only two, vinblastine and vincristine, were suitable for clinical use (Johnson *et al.*, 1963). These two differ only by an aldehyde group in the second, replacing a methyl group in the first. They both cause metaphase arrest and vinblastine interferes with transfer RNA, but details of their biological actions are unknown. Vinblastine is a valuable drug in the treatment of Hodgkin's disease and has a place in that of choriocarcinoma (Cutts *et al.*, 1960; Wright *et al.*, 1963; Scott, 1965; Fairley *et al.*, 1966). Vincristine in combination with prednisolone is the most effective primary treatment for acute lymphatic leukaemia (Evans *et al.*, 1963, Acute Leukaemia Cooperative Group B, 1963). It is of limited value in reticulum cell sarcoma, Hodgkin's disease, and myosarcoma (Whitelaw *et al.*, 1963; Shaw and Bruner, 1964). It is powerfully neurotoxic.

Antineoplastic Antibiotics

It is perhaps a matter for surprise that so many antibiotics possess antineoplastic activity. Unacceptable toxicity often forbids their therapeutic use, but four deserve consideration.

The actinomycins were an early product of Waksman's studies of soil microbiology, which later led to the discovery of streptomycin. They are formed during the growth of various *Streptomyces* species and most are mixtures of closely related chemical substances. Actinomycin C (Sanamycin) formerly had some reputation in Hodgkin's disease (Brockman and Grubhofer, 1950). Only actinomycin D is now in use. It is believed to link with DNA, obstructing RNA and protein synthesis. Its main value is in the treatment of Wilms's tumour in children and in choriocarcinoma and rhabdomyosarcoma (Pinkel, 1959; Farber *et al.*, 1960; Bailey *et al.*, 1961; Hertz *et al.*, 1964).

Mitomycin C, isolated from cultures of *Streptomyces caespitosus* in Japan (Hata *et al.*, 1956), has been used mainly in that country, where it is claimed to be effective in chronic myeloid leukaemia and gastrointestinal carcinoma. It inhibits synthesis of DNA but is also a monofunctional alkylating agent (Manheimer and Vital, 1966; Moertel *et al.*, 1968).

Mithramycin is produced by the growth of *Streptomyces tanashiensis*. It is a near specific in some patients with embryonal cell carcinoma of the testis, and complete regression has been recorded on many occasions. Its toxicity is serious and in one group 4 out of 14 patients died of gastric haemorrhage (Brown and Kennedy, 1965; Koons *et al.*, 1966; Ream *et al.*, 1968).

Daunorubicin (rubidomycin, daunomycin) is recovered from cultures of two strains of *Streptomyces, caeruleorubidus* and *peucetius* (Dubost *et al.*, 1963). It interferes with the synthesis

of DNA and RNA by combining with preformed DNA. Daunorubicin causes profound marrow depression and is cardiotoxic in any but the small doses now in use. It is undoubtedly the drug of choice in the treatment of acute myeloblastic leukaemia (Di Marco *et al.*, 1963; Tan *et al.*, 1965; Jacquillat *et al.*, 1966; Malpas and Scott, 1968; Boiron *et al.*, 1969; Bornstein *et al.*, 1969; Goudemand *et al.*, 1969), and used in combination with cytosine arabinoside has given 60% of complete remissions in adults, the highest rate yet recorded (Crowther *et al.*, 1970). A closely related antibiotic, adriamycin, has been recovered from cultures of a mutant strain of *Streptomyces peucetius*. Its range of action and its toxicity are similar to those of daunorubicin, but smaller doses are effective (Bonadonna *et al.*, 1969).

Other Antineoplastic Drugs

The final group contains a few agents which defy classification. Historically the first is urethane. Recognized as having antineoplastic activity in 1946 (Haddow and Sexton, 1946) and believed to interfere with pyrimidine metabolism, it was once used in the treatment of chronic myeloid leukaemia and myelomatosis. A closely related compound, hydroxyurea, inhibits the reduction of cytidine diphosphate to deoxycytidine diphosphate. It is probably converted in vivo to hydroxyurethane. It has proved valuable in the treatment of chronic myeloid leukaemia resistant to busulphan (Kennedy and Yarbo, 1966).

In the search for new monoamine oxidase inhibitors a series of methylhydrazines was synthesized, and in 1963 one, now known as procarbazine (Natulan), was found to have antineoplastic activity (Bollag, 1963; Bollag and Grunberg, 1963). It suppresses mitosis by prolonging interphase, causing a high percentage of chromatid breaks. In vitro it combines with DNA (Bollag, 1965). It is an effective drug in the treatment of Hodgkin's disease, but it has little effect on solid tumours or in leukaemia (Martz, 1964; Kummer and Bucher, 1965; Scott, 1965; Backhouse and Sicher, 1966; De Vita *et al.*, 1966; Fairley *et al.*, 1966; Hansen *et al.*, 1966).

The last agent to be discussed, L-asparaginase, is of interest more for its theoretical implications than for its therapeutic efficacy. It is an enzyme which breaks down the amino-acid L-asparagine into aspartic acid and ammonia. Asparagine has long been recognized as essential to all mammalian cells. It is synthesized within the cells of the higher animals, which are thus independent of an external supply. Clementi (1922) found no asparaginase activity in any human or animal sera except those of the guinea-pig and related species. Kidd (1953) noted that the serum of guinea-pigs, but of no other animals, inhibited the growth of transplanted lymphoma in mice, and it was later shown that cells of the Walker rat carcinoma 256 would not grow in tissue culture without the addition of asparagine (Neuman and McCoy, 1956). Not until 1961 was Broome able to knit together the loose ends and produce evidence that the asparaginase of guinea-pig serum was responsible for its anti-lymphoma effect (Broome, 1961, 1963).

The explanation generally accepted is that some neoplastic cells are unable to synthesize asparagine, and become dependent on external sources. Asparaginase cuts off the supply by destroying the body pool of asparagine. The finding of low levels of asparagine-synthetase in certain tumours lends support to this hypothesis. The theoretical interest of this observation can hardly be exaggerated; it was the first conclusive demonstration of a metabolic difference between normal and malignant cells. Its application to practical therapeutics presented difficulties. The serum from 4,000 guinea-pigs would be the daily requirement for each patient, but only one child was ever treated in this fashion (Dolowy *et al.*, 1966), for in 1964 another source of the enzyme was found in cultures of *Escherichia coli* (Mashburn and Wriston, 1964), and later in those of *Erwinia carotovora*.

Asparaginase will induce complete remission in 50-60% of children with acute lymphatic leukaemia (Tallal *et al.*, 1970) and in about 10% of patients with the acute myeloid form. It will often clear the peripheral blood of primitive cells in a few days (Beard *et al.*, 1970), but resistance develops rapidly. It has some effect on lymphosarcoma. It is valueless in Hodgkin's disease and solid tumours (Hill *et al.*, 1967; Oettgen *et al.*, 1967; Burchenal and Karnofsky, 1970; Clarkson *et al.*, 1970). For all its interest, asparaginase is not a therapeutic agent of great value.

Selection of Chemotherapeutic Agents

This closes my catalogue of drugs. By the end of the year 1967 88,550 compounds had been screened for antineoplastic activity in the United States alone. In all some two dozen have established their therapeutic value. It is perhaps permissible to ask whether this paltry harvest is commensurate with the financial outlay.

If we grade neoplastic disease by its response to chemotherapy we can recognize a group in which notable success has been achieved. This includes the leukaemias, the lymphomata, Wilms's tumour, and neuroblastoma as well as the solitary instance in which cure can reasonably be claimed, choriocarcinoma. Secondly, there are some cancers, particularly of the ovary, lung, and breast, in which chemotherapy is often followed by decrease in size of the tumour mass and short-lived improvement in symptoms. Finally, there is the large group of "solid tumours" in which at best only the most evanescent benefit is obtained.

The clinician, as I have already said, is forced by circumstances to judge chemotherapy by practical standards; the trivial changes which suffice to encourage the laboratory worker offer but cold comfort to the patient dying of cancer or to his medical attendant. The experimentalist wields a different yardstick, and it must not be thought to imply criticism of his endeavours over the past 25 years when I say that only to patients in the first group does chemotherapy offer worth-while benefit.

For many years it was accepted doctrine that cancer cells divided more rapidly and more frequently than healthy cells, and that this behaviour explained the growth of tumours. On this assumption methods of screening have been devised specifically to select drugs which impede cell division. All those that are active achieve this end by inhibiting replication of DNA by alkylation, or combining with it in some other way, or by blocking metabolic pathways essential for its synthesis. None kills the cancer cell because it is a cancer cell, but because, like other cells, its life revolves around DNA. Thus all our drugs act by virtue of their antimitotic effect, which is exerted indifferently on healthy and neoplastic cells. Moreover, using the methods of selection that have been developed over the past 25 years, we cannot anticipate the discovery of agents with a different mode of action. Indeed, asparaginase is the only drug which may be said to have some degree of specificity.

Basis for Chemotherapy

Although we must accept the inadequacy of the antineoplastic drugs at our command, they are all we possess, and it is therefore of the first importance to use them in the most effective way we can. Thinking has been confused in the past; the tacit, even unconscious, assumption that cure is impossible has been a barrier to advance; but, however ineffectual our efforts, cure must be our aim, and to achieve it every cancer cell in the patient's body must be killed. Some recent observations are relevant to this problem.

Studies in cell kinetics have led us to reconsider some of our traditional views on the growth of tumours. Until recently it had been assumed that cancers grow because malignant cells divide more rapidly than their healthy counterparts. This

is now known to be untrue (Baserga, 1965). A tissue, healthy or malignant, increases in size when the volume added by mitosis exceeds that lost by cell death. In healthy tissue the two are equal and size is constant. In tumour growth the increase in volume must be due either to increased mitosis or to decreased cell loss. The potential doubling times of human malignant cells range from less than 24 hours for those of Burkitt's lymphoma (Cooper *et al.*, 1966) to 90 days for those of carcinoma of the breast (Johnson *et al.*, 1960). These compare with doubling times of 15 to 18 hours for healthy human normoblasts and 25 hours for mucosal cells from the rectum (Cole and McKalen, 1961). If there is no constant increase in cell proliferation, growth must be due to decreased cell loss. There is evidence that the balance is tipped in this fashion; though the proportion of cells added by mitosis which perish spontaneously remains remarkably high, lying between 50 and 99% (Iversen, 1967; Steel, 1967), the discrepancy is enough to account for a tumour's growth. Cancer should perhaps be regarded not so much as a disease of cellular proliferation as one of cellular accumulation (Iversen, 1970).

Observations on transplanted L 1210 leukaemia in mice (Skipper *et al.*, 1964, 1965) as well as in Hodgkin's disease (Johnson and Brace, 1966) and choriocarcinoma (Bagshawe, 1968) have shown that a given dose of an antineoplastic agent kills a constant percentage of malignant cells irrespective of their total number, and that the survivors continue to divide at the previous rate. Models can be devised to show the effects of antimitotic agents on cancer cell populations. For instance, a single dose which reduced a malignant cell population of 10^4 by log 4 would result in 99·99% of the cells being killed, but if the original population was 10^6 it would be reduced to only 10^2.

If the drug used is an antimitotic, and if it is 100% effective, every mitosis will lead to cell death and the rate of destruction of a malignant cell population will be directly related to the frequency of mitosis. That is, the doubling and halving times would be equal. Bagshawe (1968) has shown that, making these assumptions and provided that the percentage of cells killed daily remained constant, a malignant cell population of 10^{10} would be reduced to zero in 35 days if the cell doubling time was 24 hours, but not for 1,750 days if the doubling time was 50 days.

This scheme takes no heed of cell loss or of the effects of the antimitotic drugs on healthy proliferating tissues. The most vulnerable and the most important of these last are the bone marrow and the mucosa of the alimentary tract. In terms of cell kinetics the antimitotic agent exerts its effect on the normal proliferating stem cells, while at the same time loss of mature functional cells continues. Depletion is likely to be rapid and profound. Therefore, if high doses are used treatment must be intermittent to permit the normal tissues to recover.

The factor of cell loss removes from the realm of impossibility the task of eliminating a malignant cell population. Bagshawe (1968) calculated that when intermittent treatment is applied with the duration of therapy and the interval between courses in the ratio of 1:2, if cell loss exceeds two-thirds of the gain by mitosis in the interval phase the population would be reduced by the amount of that excess.

There is reason to believe that different drugs exert their effect at different points in the mitotic cycle. The action of nitrogen mustard is directed against all cells, whether resting or in cycle; of 5-fluorouracil, actinomycin D, cyclophosphamide, and melphalan against cells in all stages of the cycle, but not against those in G_0; and of vinblastine, vincristine, methotrexate, and cytosine arabinoside against a single phase of the cycle only, that of DNA synthesis (Bruce *et al.*, 1966). A point of practical importance is that some 20% of normal haemapoietic stem cells are in G_0 and thus are spared by agents of the last two groups (Bruce and Meeker, 1965).

Another important development is the use of several antineoplastic agents simultaneously. The theoretical basis for such combination chemotherapy is obvious enough. The maximum acceptable dose of any drug depends on its toxicity. If two or more drugs are known to be effective and their toxic effects differ each can be given in maximum dosage summating their therapeutic actions but not their toxic effects. The value of combination chemotherapy was first established in the treatment of acute lymphoblastic leukaemia in children (Freireich and Frei, 1964) and of Hodgkin's disease (Perry *et al.*, 1967).

Practical Conclusions

These observations raise many important issues, theoretical and practical. We have allowed ourselves to become obsessed by DNA and mitosis. In exploiting so lavishly the antimitotics we have tended to neglect other directions from which a pharmacological attack on cancer might be mounted. The phenomenon of "cell loss" demands closer attention; if it could be increased the effect on a tumour would be as great as that of preventing cell division. For years metabolic differences between malignant and healthy cells have been postulated; the story of asparaginase shows that at any rate one such difference does exist. It will be an encouragement to continue the search for others.

Of more immediate relevance are the practical conclusions we may draw, which will enable us to use the drugs we possess more effectively.

There is probably no longer a place for continuous administration of single agents in low dosage. If the bone marrow were invulnerable continuous treatment would be logical when the drug's action was independent of the cells being in cycle. Intermittent high doses at intervals, depending on the cell doubling time, is more likely to be effective with drugs active only on cells in cycle, particularly when the activity is directed against one phase. Chemotherapy, however, is limited by its effect on healthy proliferating tissue: bone marrow hypoplasia is inevitable, but its severity and the degree to which the immune mechanisms are suppressed are both less with intermittent than with continuous treatment (Mathé *et al.*, 1970). There is no question that intermittent high-dosage combination chemotherapy is far more effective, at any rate in the short term, than the conventional methods. The results in acute leukaemia (Crowther *et al.*, 1970) and in stage III and IV Hodgkin's disease (Nicholson *et al.*, 1970) are an indication of what we may expect.

The final point which emerges is that treatment must be started early and that it must be prolonged. What is euphemistically called "remission" does not mean that all the malignant cells have been destroyed, only that there are not enough survivors to provide clinical evidence of their continued existence. For what length of time we should persevere with chemotherapy it is impossible to say until more clinical evidence has accumulated or until we can find, as in choriocarcinoma, some biochemical index of the tumour's persistence. To form any judgement we should need to know the cell doubling time, the rate of cell loss, the original number of tumour cells, and what percentage of cells were killed with each course of treatment. Until we can be provided with such information we are forced to depend on clinical experience.

Envoi

In this lecture I have perforce considered the chemotherapy of cancer in isolation, as if we would in time possess the magic elixir which would cure all neoplastic disorders. It is perhaps wise to remind ourselves that not only is this unlikely but that chemotherapy is only one method—and admittedly a not very effective one—of treating the patient with malignant disease. Surgery, radiotherapy, and

hormone treatment still reign supreme and immunology is close behind. Nevertheless, there are many situations where chemotherapy is the only practicable treatment, and others where it is a valuable adjunct to the old-established methods. It will not be long before it can claim acceptance to equal partnership with them.

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Electroencephalographic Prediction of Fatal Anoxic Brain Damage After Resuscitation from Cardiac Arrest

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Summary: Ninety-three electroencephalograms (E.E.G.s) were recorded within a week of cardiac resuscitation from 41 patients in whom the subsequent outcome was known to be either recovery of cerebral function or death with associated pathological evidence of gross anoxic brain damage. A statistical analysis of observations on these E.E.G.s yielded a discriminant function for predicting death or survival. Predictions based on each of the 93 individual E.E.G.s would have been correct in 92 and at a confidence level better than 99%. The same discriminant function was found to be applicable to a further 19 patients who died but did not undergo neuropathological studies and to 33 others in whom the clinical picture was complicated by such factors as uraemia or head injury. Thus it seems that the presence or absence of fatal brain damage after cardiac arrest can be reliably predicted from E.E.G.s taken within a week of resuscitation. An estimate of the probability of survival is now routinely included in the clinical report on each E.E.G. taken after cardiac arrest.

Introduction

Studies of the electroencephalogram (E.E.G.) after cardio-respiratory arrest and subsequent resuscitation are chiefly concerned with the isoelectric or "flat" tracing and its ethical and medicolegal implications for the pronouncement of death (Jouvet, 1959; Arfel and Fischgold, 1961; Bickford *et al.*, 1965; Rossoff and Schwab, 1968). Some authors, however, describe E.E.G. signs which may distinguish various types of outcome, with the aim of identifying patients who are capable of useful survival (Hockaday *et al.*, 1965; Pampiglione and Harden, 1968; Prior and Volavka, 1968). While the definition of death remains a fertile topic of ethical debate, the prediction of outcome after cardio-respiratory arrest and resuscitation appears a more profitable subject for scientific inquiry.

After Pampiglione's (1962) description of E.E.G. abnormalities which may follow cardiac or respiratory arrest, Hockaday *et al.* (1965) showed that death or survival could be predicted by means of the E.E.G. with a reliability of the order of 80%. Pampiglione and Harden (1968) achieved a similar success rate in children. We have for some years tried to apply the criteria described by Hockaday *et al.* (1965) and, more recently, used those of Prior and Volavka (1968) and of Pampiglione and Harden (1968). Many E.E.G.s seem to be unclassifiable, and in any event the accuracy of prediction does not meet the requirements of the clinical situation. All the above methods involve grading records along a simple scale of increasing abnormality, on the basis of only a few features—chiefly frequency and amplitude—thereby discounting much of the information ordinarily used in assessing an E.E.G.

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Methods

A method of visual assessment and coding was developed to provide a detailed description of any E.E.G. which might be obtained after resuscitation. Fifty-eight tracings from a pilot study at St. Bartholomew's Hospital were examined by one of us (C.D.B.) without reference to clinical information, and scored on 49 variables which described the presence, prominence, and distribution of a wide range of E.E.G. phenomena. Two other variables were admitted—the state of awareness during the recordings, as indicated by neurological evidence, and the time elapsed between resuscitation and the E.E.G. A preliminary statistical assessment suggested that this range of information might provide a satisfactory basis for distinguishing patients who died from those who survived. Training sessions were then carried out to establish an acceptable level of reliability between two observers (C.D.B. and P.F.P.). These observers then applied the same system of rating to all E.E.G.s taken after resuscitation at the London Hospital during the years 1964-8. The result of the analysis of these records is presented here.

Patients

During the five-year period 127 patients were referred to the London Hospital E.E.G. department because they had failed to regain consciousness rapidly after resuscitation from circulatory or respiratory arrest. In 93 of these subjects legible tracings were obtained within seven days of resuscitation and there had been adequate documentation of the arrest and of the subsequent clinical course. Ninety were adults aged 18 to 89 and the remaining three were less than 10 years old. The 93 patients were divided in three categories (Table I).

Group A.—These 41 adult patients met the following criteria: (1) cardiac arrest was known to have occurred; (2) there was no associated disorder considered likely to complicate the E.E.G.