There was good correlation between radiology and endoscopy in diagnosing duodenal deformity, but precise diagnosis of active ulceration requires direct vision at endoscopy.[6]

Should barium-meal examinations be abandoned as initial investigations in dyspepsia and replaced by endoscopy? The lack of trained staff and equipment for endoscopy in most areas at the district general hospital level makes this an unrealistic suggestion. This study emphasizes the importance of the availability of an endoscopy service for the investigation of the upper digestive tract as already recommended by the British Society for Digestive Endoscopy.[7] General-practitioner clinical assistants can contribute greatly to providing an adequate endoscopy service, but even with more staff the endoscopy department would not be able to carry out the many investigations for dyspepsia currently performed in the *x*-ray department. Moreover, initial screening by a combined barium-meal examination and cholecystogram with subsequent endoscopy in selected patients will provide the most accurate diagnostic approach to the problem of dyspepsia.

## Conclusions

Dyspepsia is a common complaint, the numbers seen in this study being confirmed by previous larger surveys. Many patients with dyspepsia have a specific lesion and in many the symptoms are severe enough to require surgery.

Patients with specific lesions of the oesophagus, stomach, or duodenum may remain undiagnosed unless an endoscopy service is available. Thus, endoscopy services, based on district general hospitals, need to be further developed. The appointment and training of general-practitoner clinical assistants can contribute to the provision of an adequate service.

Nevertheless, the combination of a cholecystogram with the barium-meal examination will avoid the delays in diagnosis which result if the investigations are ordered separately.

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# *Today's Treatment*

# Blood and Neoplastic Diseases

## Rational Approach to the Chemotherapy of Human Malignant Disease—II

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The usual way of measuring a response to chemotherapy in man is to assess the reduction in tumour size and improvement in the patient's general condition. Unfortunately, many types of tumour do not respond to chemotherapy using these criteria, but it must not be inferred that the therapy is ineffective in killing many tumour cells. Data on the volume of a tumour are unreliable when used as the sole end-point for estimation of the fraction of tumour cells killed by therapy.

Tumour volume studies can underestimate tumour cell kill by several orders of magnitude. The studies of the hamster plasmacytoma response to cyclophosphamide have shown the difficulties.[1] Bioassays showed that tumour cell kill after a single dose of cyclophosphamide was rapid (a few hours), but a change in the tumour mass was not noticed for several days and the regression nadir was not reached until after one to two weeks or more. By this time much viable tumour had regrown and the number of viable tumour cells could approach that of untreated controls even though the total mass was less.

A reliable estimate of the number of remaining viable tumour cells would be of immense importance in man, but there are few human tumours in which this can be made. Gestational choriocarcinoma and myeloma are two examples. Assay of chronic gonadotrophic hormone excretion in patients with choriocarcinoma has proved of great value in controlling chemotherapy in this disease. An effective drug regimen becomes quickly apparent, and continuing it can reduce the viable cell population to a level enabling the patient to be cured. In spite of this the tumour masses as observed—for example on chest *x*-ray film—may take a year or more to resolve finally after adequate chemotherapy. In myeloma serial estimations of myeloma protein production can also give a useful indication of response and allow the continued development of useful chemotherapy.

One of the most important advances which could be made concerning solid tumours in man would be the development of marker systems for assessing accurately the amount of viable tumour. Potentially useful chemotherapy will be overlooked if tumour mass is the only criterion of response.

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### Drug Resistance

Resistance to a chemotherapeutic agent may be considered under two main headings: primary and acquired resistance, which together constitute the major problem in cancer chemotherapy. The experimental approach in man has largely been directed against the problem of acquired resistance, and the systems involved have been found to be highly complex.

Several mechanisms may be operative, such as selective killing of a sensitive population leaving resistant cells, or an adaptive change by the cancer cell. Bresnick[2] has listed some of the possible adaptive changes: inhibition of membrane transport; a change in the confirmation of an enzyme rendering it insensitive to the drug; deletion of any enzyme necessary to activate the drug; detoxification of the drug to an inactive compound (by cancer cell or normal issues); an increase in concentration of a metabolite which can overcome the biochemical lesion produced by the drug; an increase in concentration of the target enzyme; a reduced requirement for a metabolite which is a product of the inhibited reaction; and an alternative metabolic pathway which is not inhibited by the drug may develop in the resistant cells.

Changes in tumour cell proliferation is another suggested mechanism for the emergence of drug resistance, and is probably an important mechanism in some tumours. In patients with chronic granulocytic leukaemia (C.G.L.) or myeloma, for example, the disease frequently terminates in a more aggressive form. In C.G.L. this involves a transition to an acute blast cell crisis with a rapid proliferation of myeloblasts similar to A.M.L. Drugs, such as busulphan, which are effective in controlling cell proliferation in C.G.L., are ineffective at this time, and phase-dependent agents, such as vincristine, produce better results.

In view of the changes which occur in proliferation rates as the tumour mass enlarges, it should not be assumed that the response of a tumour in its earliest stages will be similar to that when large amounts of tumour are present late in the disease. In practice, the tumour usually proves to be difficult to treat in the latter situation, and both considerations suggest that if chemotherapy is the treatment of choice it should be used early before the tumour mass is excessive.

An additional possible mechanism for the development of resistance is that receptors for a chemotherapeutic agent (for example, hormone receptors) may vary in concentration within a tumour cell and may be responsible for a different response rate. Most of these mechanisms have been studied in animal tumours, because drug resistance is difficult to define in man. A tumour which fails to respond to a drug given in one way may show a dramatic response if the schedule of administration is altered. To date there has been no convincing evidence provided in human cancer for a particular defect being responsible for drug resistance, though several possible mechanisms have been investigated. Resistance to cytosine arabinoside in patients with A.M.L. provides an example of the sort of studies being carried out. In patients who have had previous treatment with cytosine arabinoside and are less responsive to this drug, the leukaemic cells contain more cytosine deaminase, which detoxifies it. For the correct mechanism of resistance to be determined, however, it will be necessary to study many other features, such as membrane transport of the drug, thymidine kinase activity, and leukaemic cell proliferation rates. Possibly several of the mechanisms of resistance listed previously operate in the same patient.

Several important questions have be answered about the problem of primary drug resistance. The part played by defective drug membrane transport, metabolic alterations, poor blood supply, and proliferative characteristics in naturally resistant solid human tumours could be determined with suitably designed experiments. Measurement of drug sensitivity in young, rapidly growing tumours compared with older larger tumours, would provide useful information. A comparison between primary and metastatic tumours would also be of great value.

### DRUG DIFFUSION

Drug diffusion is one of the main problems limiting the value of chemotherapy in solid tumours. The use of drug analogues which competitively reverse the effect of a chemotherapeutic agent may be important since slow diffusion of the analogue into the tumour works in favour of the host. An additional factor to consider is the reduction in proliferation rate of tumour cells further away from the blood supply (see table). The problems associated with poor drug diffusion will increase with the tumour mass. High-dose methotrexate has been used with these problems in mind. The toxicity of this drug is proportional to the time during which it acts, and extremely high doses can be used for 48-hour periods. The high concentration allows diffusion into the tumour. At 48 hours the effects are reversed with folinic acid but the slow diffusion into the tumour on this occasion works in favour of the host and against the tumour.

*Cell Kinetics in Transplanted Mouse Mammary Tumour*[5]

| | Region Near Blood Vessel | Intermediate Region | Regions Near Necrosis |
|---|---|---|---|
| Mitotic index | 4·3 ± 0·4 | 2·5 ± 0·3 | 0·6 ± 0·2 |
| Labelling index | 50·0 ± 2·5 | 29·6 ± 4·8 | 10·3 ± 3·4 |

Drug resistance may be present when the tumour cells are in a sanctuary such as the central nervous system (C.N.S.). This is the case, for example, in A.L.L. of childhood, where without appropriate prophylactic chemotherapy and radiotherapy to the C.N.S. meningeal involvement develops in about half of patients. Prophylactic C.N.S. treatment is now being tested in several tumours where the incidence of C.N.S. involvement is high.

The emergence of drug resistance in tumours has been exploited therapeutically. Tumour cells resistant to methotrexate frequently have increased levels of the enzyme dihydrofolate reductase and such cells are likely to be selectively sensitive to agents such as the homofolates which are activated by this enzyme. Studies with mouse leukaemia have shown increased sensitivity to dihydrohomofolate in tumours with increased levels of dihydrofolate reductase. Another suggestion has been made that 5-fluorocytosine, which can be activated by cytosine deaminase, may be useful therapeutically in leukaemias resistant to cytosine arabinoside which possess increased levels of this enzyme.[3] In future it may be possible to predict primary resistance of a tumour using biochemical characteristics. An example of this has been provided by experiments showing that adenosine deaminase inactivates the anti-tumour agent ß-arabinofuranosyladenine (Ara-A) and that experimental tumours with high levels of the enzyme are naturally resistant to the drug.[4]

### Guidelines

There can be no general approach to the chemotherapy of the many different forms of human cancer. Nevertheless, guidelines can be suggested using the principles previously referred to. The approach to the chemotherapy of generalized malignant disease in man can be conveniently divided into five parts: remission induction; consolidation; maintenance; late intensification; and stopping chemotherapy.

Remission induction in the lymphomas and acute leukaemias usually consists of treatment with a combination of drugs until the patient is free from apparent disease and there is a return to normal health. At this stage the disease will return in a large proportion of patients if no further treatment is given. The way in which this further treatment should be given is controversial and varies according to the disease being treated. Most authorities advise further treatment with the agents that produced the remission. The role of maintenance chemotherapy in the treatment of the lymphomas is unknown. In Stage IIIB of Hodgkin's disease, for example, the best results have been reported using only six courses of MOPP (mustine, vincristine, procarbazine, and prednisolone), and further treatments are of controversial value. In the acute

leukaemias, however, maintenance treatment is necessary and will lead to a considerable improvement in survival and remission length.

There is a theorectical advantage in the intensive use of phase-dependent drugs when the tumour cell population is likely to be very small and the patient healthy, but its use in the clinic is controversial and is at present under study. Stopping all chemotherapy is a difficult decision, but some studies have been done in A.L.L. of childhood which show that in this disease maintenance should be carried on for at least two years.

With these techniques considerable advances have been made in the treatment of the lymphomas and acute leukaemias. In some series half the children who achieve a complete remission from A.L.L. are alive, well, and in their first remission at five years. Considerable advances have also been made in the treatment of generalized Hodgkin's disease. About 75% of patients with Stage IIIB and IV disease achieve a remission with MOPP therapy or a modification using vinblastine instead of vincristine and, half will be alive, well, and in their first remission five years later. In some patients with certain other types of cancer—particularly Burkitt's lymphoma, Wilm's tumour, and gestational choriocarcinoma—remissions have been sufficiently long to be considered cures. Unfortunately, the reasons for the long survival in some patients with cancer are conjectural and may depend less on the applied chemotherapy than host-resistance factors. Nevertheless, the results already obtained indicate that the future holds the promise that further improvements will occur for most patients with cancer and that more will have a normal lifespan using appropriate treatment.

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# *Contemporary Themes*

# Gynaecological Abnormalities found at a Cytology Clinic

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### Summary

**A survey was made of abnormalities found on pelvic examination of 2,656 women who attended for cervical smears in the three years 1967-9. Eight women had malignant cells in their smears, and 68 women pelvic tumours, four of them malignant. Severe vulvitis was common in women over 46. Many of the women who had non-malignant conditions were treated though they had no complaints. They were among the most appreciative and subsequently sought out the clinic staff to thank them. It is important that a full examination should be made by an experienced gynaecologist.**


### Introduction

The aim of this paper is to show the value of a pelvic examination carried out by a trained gynaecologist in women attending a cytology clinic. The purpose of such an examination is to diagnose malignant and premalignant disease of the genital tract and other gynaecological disorders which are the cause of chronic ill health.

### Patients and Methods

A total of 2,656 patients with ages ranging from 26 to 78 were examined (table I). There was no selection other than an expressed wish by the patient for the examination. Though initially designed to be a gynaecological survey the examination at the clinic was later extended to include a general medical assessment.

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TABLE I—*Age Distribution of Patients Examined*

| Age in years | 26-35 | 36-45 | 46-55 | 56-65 | >65 |
|---|---|---|---|---|---|
| No. (%) of patients | 90 (3·4) | 846 (31·9) | 1,165 (43·9) | 415 (15·6) | 140 (5·3) |

### Results

CYTOLOGY

The smear results are given in table II. All patients with positive smears were admitted to hospital for cone biopsy and diagnostic curettage in the first instance. Eighteen patients with abnormal smears but without malignant cells had cervical biopsies and repeat smears. None was subsequently found to have carcinoma. Four patients with positive smears had carcinoma in situ; the youngest was 30 and the oldest 66 years, and all were married with children. They were treated by extended hysterectomy. Three patients with positive smears had invasive carcinoma. They were all clinically stage 1, and aged between 42 and 49.

TABLE II—*Age and Diagnosis in Patients with Positive Smears*

| Age (years): | 26-35 | 36-45 | 46-55 | 56-65 | >65 | Total |
|---|---|---|---|---|---|---|
| Carcinoma in situ .. .. | 1 | 2 | 1 | | | 4 |
| Invasive cervical cancer .. | | 1 | 2 | | | 3 |
| False positive smear .. .. | | | 1 | | | 1 |