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# PROSPECTS IN CANCER THERAPY

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## Introduction

For those who, despite the mass of evidence to the contrary, continue to regard cancer as a single disease, progress towards effective therapy and cure must seem very slow. But for those, like myself, who regard cancer as a group of diseases with some features in common, there have been a number of encouraging observations and advances during the last few years. It is not my intention to raise false hopes or to suggest that the immediate prospects for most cancer sufferers are greatly better today than they were say five years ago. On the other hand, it would be wrong of me not to draw attention to recent work which I feel provides real grounds for satisfaction and hope.

Table I summarizes the various approaches to the treatment of cancers. The topics listed there will be considered in separate sections. But first it is necessary to mention the possibility that cancers may regress spontaneously, and the suggestion that this may be the result of immunological rejection.

## Spontaneous Regression

During the last 3 years two important books on the subject of the spontaneous regression of cancers were published, one by William Boyd (1966) the eminent American Pathologist, and one by Everson and Cole (1966), two surgeons at the University of Illinois, who over a period of many years have collected and analysed reports of cases of spontaneous regression. The latter authors were able to accept 176 cases of regression as authentic (see Table II). More than half of these were of adenocarcinomas of kidney, neuroblastomas, malignant melanomas or choriocarcinomas, and in most cases regression was not entirely a spontaneous phenomenon but followed some sort of 'interference' - therapeutic, diagnostic, or incidental - which did not itself eradicate the cancerous tissue.

TABLE : I  
APPROACHES to the TREATMENT of CANCERS

1. SURGERY	Conventional
	Transplantation
2. RADIOTHERAPY	
3. CHEMOTHERAPY	Hormones and Endocrine Ablation
	Enzymes (e.g. L-Asparaginase)
	Alkylating agents and Antimetabolites
4. IMMUNOTHERAPY	Mathé's Work
	Recent Experimental Studies
	Possibility of Protecting against Oncogenic Viruses
5. COMBINATION THERAPY	Chemosurgery
	Infusion and Perfusion techniques

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TABLE : II  
SPONTANEOUS REGRESSION OF CANCERS IN MAN

(Based on survey of world medical literature  
since 1900 by Everson and Cole, 1966)

<u>Site or Type of Cancer</u>	<u>No. of Cases</u>
Kidney (Adenocarcinoma)	31
Neuroblastoma	29
Malignant Melanoma	19
Choriocarcinoma	19
Bladder	13
Soft-tissue Sarcoma	11
Sarcoma of Bone	8
Colon and Rectum	7
Ovary	7
Testis	7
Breast	6
Other Sites and Types	19
Total	176

Boyd (1966) from a consideration of possible mechanisms concluded that immunological factors probably play the most important part in the spontaneous regression of cancers. It is thought by some that the growth and progress of cancers are always to some extent limited by immunological mechanisms. It is even suggested that for every cancer that grows there are many that are successfully eliminated by immunological mechanisms whilst they are still very small - perhaps even still at the single cell stage. In the light of present knowledge it is difficult to regard these suggestions as more than theoretical.

### **New Antigens in Tumours**

It is true that in most induced cancers in laboratory animals, the presence of abnormal antigens can be demonstrated but it is less certain that abnormal antigens are always a feature of cancers that seemingly arise spontaneously. Woodruff (1964) suggested that many or all malignant tumours possess distinctive antigens in the early stages of their life history, but subsequently these antigens may be partly or wholly deleted. Where they are not deleted, the tumours may be destroyed immunologically. If they are not destroyed before the deletion of antigens has occurred, they are unlikely to be destroyed by immunological mechanisms later.

### **Latent Cancers**

The studies of Franks (1956) on the incidence of latent carcinomas of the prostate gland give some support to the view that actively growing and disseminating cancers may occur for less frequently than small subclinical cancers. According to Franks the incidence of latent carcinomas in the prostate rises throughout life to reach nearly 50% in men over 80. However, this observation - even if one accepts that it is possible on purely morphological grounds to detect a 'latent carcinoma' - hardly supports Woodruff's suggestion. If the reason why the cancers seen by Franks do not grow is immunological rejection by the host why are the lesions not rejected?

### **Increased risk of development of cancers during prolonged immunosuppression**

#### **(a) Laboratory studies**

Recently evidence of the importance of immunological mechanisms in fighting the growth and spread of cancer has come from two sources (Table III). The first is from the laboratories of the Imperial Cancer

TABLE: III  
IMMUNOSUPPRESSION AND CANCER

Species	Treatment	Effect	Probable Explanation	Reference
Mouse	Thymectomy and A.L.S.	Development of polyoma-virus type cancers	Immunosuppression permitted polyoma-transformed cells to grow into cancers	Gaugas et al, 1969
Man	Kidney transplantation and immunosuppression by various drugs	(1) Development of reticulum-cell sarcomas (2) Unexpected development of donor-type cancers	Immunosuppression permitted cells transformed by unidentified virus to grow into cancers Intact immune mechanisms in donors restrained growth of small tumour emboli in kidney until it was transplanted to immunosuppressed recipient	Lancet, 1968 Doak et al, 1968 Lancet, 1969

Research Fund and of the Medical Research Council at Mill Hill, London (Gaugas et al, 1969). These workers destroyed or seriously depleted the immunological capacity of adult mice by removing their thymuses and treating them with anti-lymphocytic globulin (ALS IgG). A high proportion of the mice so treated developed cancers of types normally associated with a tumour-inducing virus - the polyoma virus. Although other explanations are possible, it seems most likely that the extreme immunosuppression brought about by thymectomy and treatment with ALS permitted polyoma-induced tumour foci, that are normally destroyed or lie dormant and unable to grow, to enlarge and flourish as active cancers.

#### **(b) Observations on recipients of kidney transplants**

The other source of evidence that favours the view that immune mechanisms are important in cancer stems from observations on recipients of kidney transplants. Over 2000 such operations have been performed throughout the world (Human Kidney Transplant Registry Report, 1968). The success of the operation depends on effective long-continued immunosuppression. To date six cases of transfer of unsuspected malignant disease from the donor to the recipient have been reported. The growth of the transplanted tumour cells in the immune-suppressed host is not surprising but the presence of inobvious tumour cells in the transplanted kidney - an organ in which metastases tend to occur late rather than early - is somewhat surprising. A possible explanation is that before transplantation the growth of small tumour emboli in the kidneys was suppressed by immune mechanisms in the donor. At least 7 recipients of kidney transplants are reported to have developed reticulum cell sarcomas (Lancet, 1968; Doak et al, 1968). As in the laboratory experiments of Gaugas et al (1969) the most likely explanation is that intensive immunosuppression facilitated the growth and spread of a virus-induced cancer.

#### **Implications of observations on effects of immunosuppressive therapy**

Observations on the effects of immunosuppressive therapy in man and laboratory animals pose several serious questions and have important implications in relation to the treatment of cancer. Table IV lists these questions and implications.

#### **Possible explanations for the spontaneous regression of cancers**

In the search for new ways of treating cancer, we would be foolish not to pay the greatest attention to examples of spontaneous regressions

TABLE : IV  
SOME IMPLICATIONS OF RECENT OBSERVATIONS ON EFFECTS  
OF PROLONGED IMMUNE SUPPRESSION

- (1) May be due to specific or non-specific stimulation of immune responsiveness.
- (2) Transplantation surgery combined with the need for prolonged immunosuppression may be ill advised for the treatment of cancer.
- (3) Subtotal removal or destruction of a cancer by surgery or drugs, combined with stimulation of immune defence mechanism may be effective (e.g. Burkitt's lymphoma; Mathé's work).
- (4) In the cases of Chemotherapy and Radiotherapy it may be necessary to balance benefits from tumour destruction with dangers from damage to immune mechanism.

of the disease. In the light of the evidence discussed above some possible explanation of spontaneous tumour regression may be postulated. These are shown in Table V. Neither Boyd (1966) nor Everson and Cole (1966) report any case in which interruption of the blood supply as a result of torsion or surgical interference is likely to be the mechanism responsible for regression. But there are cases in which regression has followed destruction due to massive haemorrhage into the tumour.

TABLE : V  
POSSIBLE EXPLANATIONS FOR SPONTANEOUS  
REGRESSION OF CANCER

1. Complete interruption of blood supply.
2. Interference with tumour, enables immune mechanisms to overcome a tumour.
3. Specific or non-specific stimulation of immune defences.
4. Increase in tumour-antigenicity as a result of tumour progression or microbial infection.
5. Change in hormonal status of host.
6. Operation of unidentified homeostatic mechanism.
7. Maturation (e.g. neuroblastoma).

Foulds (1954) reviewed evidence for what he called «tumour progression», or change in the behaviour of a tumour as it develops. In most instances progression is in the direction of increasing malignancy. But

the possibility of change in the opposite direction may be envisaged. An example of a related phenomenon is seen in the case of neuroblastomas. Tumour regression as a result of the maturation of neuroblasts to non-dividing neurones has been described by Kissane and Ackerman (1955).

It is well known in the case of tumours of laboratory animals that microorganisms tend to collect within the tumour tissue, perhaps because a relatively poor blood supply to the tumour protects the organisms from the host's defences. It is conceivable that an accumulation of microorganisms may increase the antigenicity of the tumour cells and render them more subject to immunological attack. All things considered it seems that change in hormonal status and immune-rejection of residual tumour tissue, after most of it has been destroyed by other means, are the most probable mechanisms of tumour regression in most instances.

It is of interest now to look at conventional methods of treating cancer - surgery, radiotherapy, chemotherapy - in the light of recent advances, in the field of immunology and of possible mechanisms involved in the spontaneous regression of cancers.

### **Burkitt's Lymphoma**

Until a few years ago the success of chemotherapeutic agents seemed to be limited by the shape of the curve that relates dose of drug and the percentage of tumour cells killed by it (see Fig. 1). In no case are 100 % of tumour cells killed by a dose that is not also lethal to the host.

Against the background of this rather unpromising concept came the surprising and gratifying reports from Africa of striking remissions and apparent cures of patients with Burkitt's lymphoma in response to cytotoxic drugs. Sometimes these good effects followed treatment with doses of drugs too low to kill anything approaching 100 % of the tumour cells. Indeed submaximal chemotherapy seemed more effective than maximal therapy, perhaps because the latter destroyed the host's lymphocytes and thereby weakened his immunological defences. This fact, together with the knowledge that spontaneous regression of Burkitt's lymphoma occurs occasionally, suggested that immunological rejection plays an important role. Thus the drug may kill, say, 90 % of the tumour cells, and the body's own immunological defences the remaining 10 %. If this is what happens, could results of therapy be improved even further by combining chemotherapeutic destruction, or surgical removal of the main bulk of the tumour tissue with stimulation of the patient's immunological system? Mathé and his colleagues (1967), following the



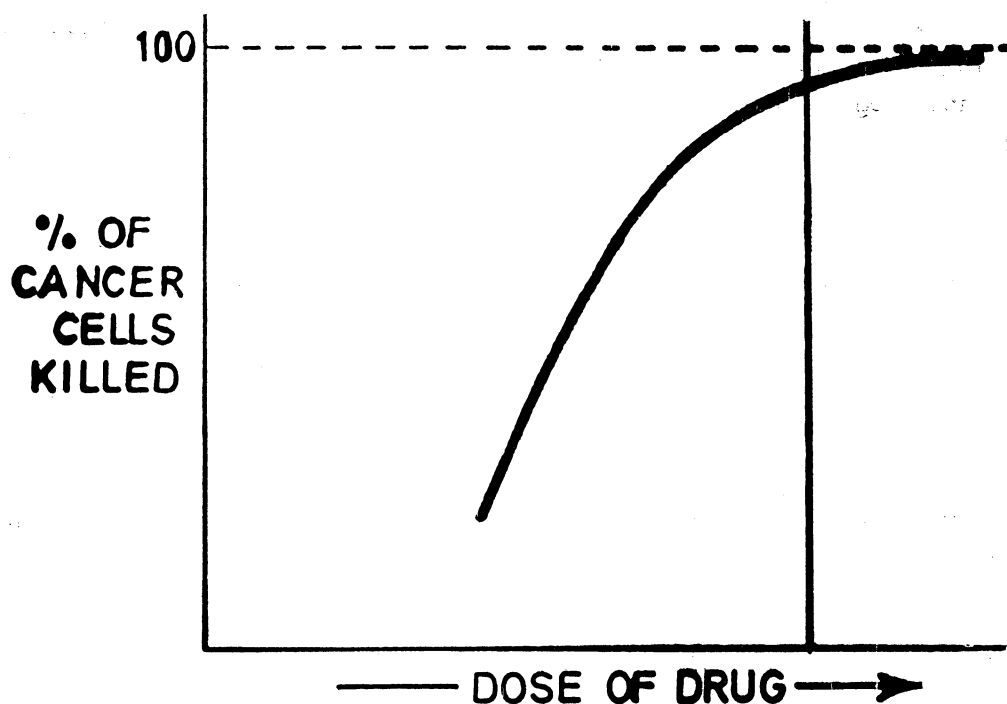


Fig. 1

Fig. 1. Maximum Tolerated Dose Of Drug.

work of Old et al (1961) developed a method of stimulating the immunological defence of patients by repeated B.C.G. vaccination. Repeated injection of oleic acid (Murphy, 1924) has been used for the same purpose. Clifford (1968) reported that by a combination of chemotherapy and/or surgery to remove the bulk of the tumour and immunotherapy with oleic acid injection and/or B.C.G. vaccination, 71 % of Burkitt's lymphoma patients can be brought into prolonged remission or cured. The comparable figure for chemotherapy and/or surgery without immunotherapy is 53 %.

#### Treatment of acute leukaemias

Can the good results obtained in the case of Burkitt's African lymphoma be achieved in the treatment of the types of leukaemia prevalent outside Africa? Corticosteroids and a wide variety of cytotoxic drugs, including both alkylating agents and antimetabolites, have proved useful in bringing cases of acute leukaemia into remission. Burchenal (1966) collected 132 cases in whom remissions persisted for more than 5 years and in some of whom permanent cure seemed to have taken place. However, prolonged remission is the exception, and in most cases the disease eventually recurs in a form that fails to respond to treatment.

It is perhaps too early to assess the effects of combining chemotherapy and immunotherapy in the treatment of acute leukaemia. Mathé et al (1967) in Paris have used repeated B.C.G. vaccination to stimulate immune responsiveness in patients previously brought into remission by chemotherapeutic agents. Some of Mathé's patients so treated have experienced prolonged remissions, but the experience in other treatment centres has been less encouraging.

### **Specific immunotherapy**

B.C.G. vaccination and oleic acid injection are examples of non-specific immunotherapy. Attempts at specific immunotherapy are still in an experimental stage. Two approaches have been used - the administration of specific antisera or vaccines and treatment with lymphoid cells.

Slight beneficial effects from the use of vaccines prepared from the patient's own tumour tissue have been recorded (Graham and Graham, 1959). Czajkowski et al (1967) reported prolonged remission in 2 out of 14 patients immunised with their own tumour cells coupled to rabbit gamma globulin and bisdiazobenzidine. Mathé et al (1967) reported long remissions in cases of acute leukaemia treated by injections with heavily irradiated leukaemic cells.

There is evidence from the laboratory (Alexander 1968) that lymphocytes in the lymph nodes draining the area of a tumour possess anti-tumour activity. If tumour tissue is taken from one animal and injected into another, lymphocytes in the nodes draining the injection site may, on introduction into the donor animal, cause tumour regression.

It must, however, be emphasised that these approaches to specific immunotherapy are still at an experimental stage. Moreover, there are theoretical dangers as well as benefits from the use of specific vaccines and antisera. As pointed out by Gorer (1961) under certain circumstances tumour cells may be protected rather than destroyed by antisera, so that their administration may be followed by enhanced tumour growth instead of regression. The introduction of foreign lymphocytes also carries a danger - the danger of graft-versus-host disease.

### **L-Asparaginase**

Before we leave the subject of the treatment of leukaemia, it is necessary to say something about the exciting story of the enzyme, L-asparaginase. The story began with the observation of Kidd (1953) that guinea-pig serum inhibits the growth of a particular form of lymphoma in mice. Clementi (1922) had previously shown that guinea-pig serum is a particularly rich source of the enzyme, L-asparaginase; and Broome

(1961) deduced that the antitumour activity of guinea-pig serum was attributable to the effect of the enzyme on tumour cells that depended for their growth on a supply of L-asparagine; The bacterium, **Escherichia coli**, was found to be a suitable source for the large amounts of enzyme needed for clinical trial. In due course complete remissions of acute leukemia in response to L-asparaginase prepared from **E. coli** were reported (Hill et al, 1967; Oettgen et al, 1967). In most cases remission has been followed by eventual relapse but better results may be expected when the enzyme is available in greater quantities and in a higher state of purity.

The importance of the discovery of the value of L-asparaginase lies in the specificity of its action and in the fact that it opens up an entirely new approach in cancer chemotherapy. If it is possible by **in vitro** tests to predict response to this enzyme, then it is reasonable to check the **in vitro** sensitivity of cancers to a range of other enzymes. It would be surprising if L-asparaginase proved to be the only enzyme to have anti-tumour activity.

### **Virus - induced Cancers**

There is as yet no unequivocal evidence for a virus-aetiology of any form of human cancer, but there is strong circumstantial evidence that viruses are involved in the causation of Burkitt's lymphoma and of the reticulumcell sarcoma developed by recipients of kidney transplants subjected to prolonged immunosuppression (vide supra). Studies in animals suggest that new antigens are especially likely to be associated with tumours induced by viruses and that these antigens are specific for each causative virus. It is tempting to deduce that the amenability of Burkitt's lymphoma to treatment is related to a high antigenicity attributable to its causation by a virus.

In this connection a recent report from Morton and his colleagues (1968) is of some interest. These workers found specific antigens in patients with melanomas. More recently still they have reported (Morton et al, 1969) tumour-specific antigens in cases of osteogenic sarcoma and soft tissue sarcoma. These reports will undoubtedly lead to a closer look at the possibility of treating such tumour by the same methods as have been found successful in Burkitt's lymphoma - that is to say by a combination of chemotherapy and or surgery with immunotherapy.

### **Choriocarcinoma**

The discovery that methotrexate could cure choriocarcinoma was at first attributed to the known need of the foetus for folic acid. This theory became less likely when other cytotoxic agents such as actinomycin D were found to be equally effective. Success was then attributed to immunological rejection after most of the tumour had been destroyed by cytotoxicity. This theory is still unproved but it is gratifying that the cure rate for this form of cancer has by the combined use of methotrexate and folinic acid been pushed up from the 30 % level, achievable by hysterectomy alone, to between 50 and 80 % (Bagshawe and Wilder, 1964).

### **Allergic disease and cancer**

Before turning to other approaches in the treatment of cancer, I feel I should bring to your attention a recent report from Scotland. According to Ure (1969), amongst a group of 140 patients in the gynaecological ward of a general hospital 28 gave a history of allergy to pollens, fur, wool or animal dander. None of these patients had cancer. On the other hand, of the 40 patients of the group who did have cancers, none gave a history of allergic symptoms. The findings suggest that the type of immune reaction that leads to allergic symptoms also protects against cancer. As is well known, the symptoms of allergy tend to decrease with age. A similar falling off in protection against the growth and spread of cancer cells may partly account for the increased incidence of cancers in later life.

### **Renal adenocarcinoma**

A recent development in the field of hormone therapy deserves special mention. It is the discovery by Bloom and his colleagues (Bloom, 1964; Bloom and Wallace, 1964; Bloom, Roe and Mitchley, 1967) that adenocarcinoma of the kidney sometimes responds dramatically to hormone administration or endocrine ablation. The kidney is not normally considered to be a part of endocrine system, but it is in fact an organ whose function is continuously moderated by the activity of hormones secreted elsewhere in the body. At present it is not yet clear which hormones are the most promising in the treatment of renal cancers, a potent antioestrogen, and certain progestational agents have both been found to have beneficial effects.

### **Breast cancer**

Opinion on the best method of treating cancers of the breast is subject to fashion. At present the pendulum is swinging away from the mutilating operation of radical mastectomy to more conservative procedures such as limited mastectomy combined with radiotherapy to the breast and draining lymph nodes.

Recently Dr Rigby Jones (personal communication) reviewed 167 cases of breast cancer treated in this way in the Royal Nasden Hospital London. The average interval between excision and start of radiotherapy was 9 days, and radiotherapy was given either at 250 kV or on the 1500 Telecaesium unit. A routine 5-field technique was used comprising a pair of opposing breast fields, an anterior supraclavicular axillary field, a posterior axillary field and a parasternal field. The average maximum dose to the tumour site and the axilla was 6,100 rads given over a period of 9 weeks. The overall 5-year survival rate was 67 % and for Stage I cases it was 76 %. The results were especially good for cancers of the inner half of the breast, for which there was a 78 % 5-year survival irrespective of stage.

These 5-year survival figures compare very favourably with those for radical mastectomy especially in the case of cancers of the inner half of the breast. Furthermore, unlike radical mastectomy, local mastectomy followed by radiotherapy is followed by little or no morbidity. Some patients have experienced slight oedema of the arm. The telangiectasia seen after 250 kV therapy is not so marked after treatment with telecaesium. Apical fibrosis of the lung, visible in chest films, gives rise to no symptoms.

### **Chemosurgery**

I am conscious of having said very little to you about what may be called conventional surgery and conventional radiotherapy. The main reason for this is that I am not a surgeon nor a radiotherapist. A subsidiary reason is that I share the view that the possibilities of improving the results of cancer treatment by these methods alone are limited. Better surgical methods and improved techniques of calculating doses and of delivering irradiation have led to marginal improvements in results, especially in the treatment of cancers that are not already widely disseminated, but for cases in which dissemination has already occurred, improvement in surgical and radiotherapeutic techniques has little to offer even in the form of more worthwhile palliation.

There is, however, one technique that I think is worthy of special mention. I refer to a method developed many years ago in Madison, Wisconsin by Dr Frederic Mohs. The method is particularly applicable to the treatment of skin cancer and involves a combination of surgery, local destruction by a chemical agent and close pathological control. First, the major of a tumour is removed surgically. Next the base of the wound is treated with a preparation containing zinc chloride. Zinc chloride kills cells and at the same time fixes them in a way suitable for histological examination. The concentration of zinc chloride applied determines the depth of its penetration into the tissues. The day after treatment with zinc chloride a thin layer of tissue is removed from the base of the wound and examined systematically under the microscope for tumour tissue. Whenever tumour extension is found zinc chloride is reapplied and the process repeated until the whole base of the tumour area is free from tumour tissue. The method is precise and time-consuming but has a definite place in the treatment of a small proportion of cases of skin cancer notably sclerotic basal-cell carcinomas with poorly defined margins, tumours near anatomically important structures such as the nasal ala or orbital canthus, and tumours that have recurred after surgical removal or radiotherapy. Mohs (1956) claimed a 95 % 5-year cure rate for previously treated basal-cell carcinomas and a 99 % 5-year cure rate for previously untreated lesions.

It should be emphasised that that pathological control is an essential part of the method and that 'blind' treatment with zinc chloride or by any other means (e.g. other chemical agents or electrodissection and curettage) is not being recommended. Incidentally, I am strongly opposed to the local application of cytotoxic drugs such as 5-fluorouracil or methotrexate in the treatment of skin cancer as advocated by Belisario (1965). Not only is treatment far less effective than by surgery or radiotherapy, but there is a risk of death from systemic toxicity.

The advances in the treatment of cancers that I have discussed are summarized in Table VI.

### **Earlier diagnosis**

Irrespective of how better methods of treating cancer are to be achieved, there can be little doubt that much is to be gained by earlier diagnosis. Two reports are of interest in this respect. The first is from the Cancer Detection Centre at the University of Minnesota where 6,800 women have undergone 32,000 annual examinations over a period of 20 years (Gilbertsen, 1966). Among 47 cases of breast cancer detected, there

TABLE : VI  
RECENT ADVANCES IN CANCER THERAPY

1. Burkitt's lymphoma	— Chemotherapy + Immunotherapy
2. Choriocarcinoma	— Chemotherapy
3. Acute leukemia	— L-asparaginase ? Immunotherapy
4. Renal Adenocarcinoma	— Hormones and endocrine ablation
5. Breast Cancers	— Limited surgery followed by radical radiotherapy
6. Skin Cancers	— Chemosurgery

was spread to lymph nodes in only 9. Crude 5-year survival rates for node-negative and node-positive patients were 75 % and 96 %, respectively. Crude 10-year survival rates were 40 % and 88 %. After correction for age by an actuarial method the survival rates at 5 years and 10 years were close to 100 % for both node-negative and node-positive patients.

In Japan, where gastric cancer is the most frequent form of malignant neoplasm numerous attempts are being made to diagnose the disease in its early stages. These include periodical radiological and endoscopic examination of middle aged individuals without symptoms. Five-years survival rates of up to 98 % have been achieved by these means (Kawashima, 1966).

### Concluding remarks

Reasons for expecting important advances in the ways of treating cancers are more substantial than they were ten years ago. Rapid increases in our knowledge of immune mechanisms suggests that rational and practical methods of treating cancers by various forms of immunotherapy may not be so far away. At present it seems most likely that the place of new immunotherapeutic methods will be in combination with surgery, radiotherapy or chemotherapy. It is likely that early cancers will always be easier to treat than advanced cancers, irrespective of the development of new treatment techniques. The value of newer methods of earlier diagnosis are already becoming apparent in relation to cancers of the breast, stomach and uterine cervix. The brightest prospect of all stems from a combination of earlier diagnosis and new methods of treatment.

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