Certain aspects of ovarian cancer

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INTRODUCTION

The two outstanding recent advances in Obstetrical and Gynaecological cancers have been in the field of carcinoma of cervix and chorioepithelioma. With mass cytological screening of all females at risk, backed up by a competent Gynaecological & Pathological service, cervical cancer is now a preventable disease (Stallworthy 1972). To a lesser extent, the combined approach of liberal prophylactic hysterectomy and methotrexate therapy, has very significantly reduced the incidence of chorioepithelioma and its aftermath. As these two success stories are extensively documented and well known it is proposed to mention them merely by way of introduction. For the purpose of this afternoon's discussion let us examine some of the problem areas in connection with Ovarian Cancer.

Ovarian Cancer:

Even as we reach the mid-Seventies, the outlook for patients who develop carcinoma of the ovary is almost as bleak as it has been ten years ago. Ovarian cancer continues to be a devastating disease. It looms as the killer of more adult women than any other form of female genital cancer. Despite improved operative techniques, irradiation methods with sophisticated high energy machines, and new chemotherapeutic agents, the overall poor prognosis remains. One typical series (Artner & Beck 1970) reports a 50% 5-year survival for stages IA & IB and 27.3% for Stage II. For Stages III & IV it is well below 20%.

The main reasons for such a gloomy picture for ovarian cancer are as follows:—

(1) delayed diagnosis
(2) a primary inherent tendency for ovarian cancer cells to exfoliate, and
(3) inadequate response to surgery (often incomplete because of delayed diagnosis), radiotherapy, and more recently, chemotherapy.

I propose to consider these and related issues in some detail but before that it is pertinent to point out that there is great complexity in ovarian cancer. Any evaluation would of necessity take into account clinical staging on the one hand and histological typing and grading on the other. Unfortunately, there is no clear cut correlation between the clinical course of the disease and the two groups of multiple variables.

Delayed Diagnosis:

Carcinoma of the ovary has been named the

greatest masquerader in Gynaecology, and delay in its diagnosis has been repeatedly emphasized. From the standpoint of initial symptoms and indeed ultimate prognosis, two gross types of ovarian cancer can be recognised, namely, encysted and non-encysted variety. In patients with encysted ovarian cancer, initial symptoms are usually primarily pelvic in nature and consist of pain and pressure from rapid distension and tension of the cyst wall. These symptoms occur relatively earlier, but even then they are sometimes mistaken for pelvic endometriosis, pelvic inflammatory disease, benigh ovarian cyst or laterally displaced pedunculated fibromyoma.

On the other hand, in the non-encysted or solid variety, pain from capsule tension is minimal and relevant symptoms would not occur until the intra abdominal absorbing membranes i.e. peritoneum or omentum, become involved with metastases. The initial symptoms are usually gastrointestinal in nature – abdominal distension, cramps, bloated sensation, nausea, constipation – symptoms frequently attributed to "indigestion" and very often treated with self-medication. Regretably, in carcinoma of the ovary, these symptoms too frequently herald the beginning of Stage III disease.

From these observations it is quite obvious that no significant advance in the management of ovarian cancer is feasible until newer and accurate methods for early diagnosis are available. Meanwhile, a high index of suspicion as exemplified by these two rules of thumb is the only way to improve salvage rate.

(i) a constant awareness of the possibility of ovarian cancer in female patients who present with vague symptoms of a gastrointestinal nature. This particularly applies to general practitioners and physicians who are usually the first to be consulted.

(ii) it cannot be too strongly emphasized that an adequate and competent pelvic examination should be part of the medical work-up of every adult woman. This aspect is singularly relevant as more and more women are now coming forward for a 'Pap' smear. Every woman who has an ovarian enlargement, certainly if it feels hard, should have a laparotomy or laparoscopy if available. Ovarian cancer is notoriously difficult to recognise early and by laporatomy or laparoscopy, not only may the tumour be visualised, but also a biopsy may be performed, if this is considered necessary.

What of the future? What are the approaches being currently pursued? Will there be a breakthrough for early diagnosis of ovarian cancer soon? Let us do a little crystal-ball gazing:

Tendency to Exfoliate:

Noting the tendency for ovarian cancer to exfoliate, one logical answer would be to look for cancer cells at the earliest possible moment. Periodic culdocentesis may be performed but its value is doubtful. It is unlikely for asymptomatic women to agree to such a procedure at a routine examination. Besides the volume of fluid so obtained would be small so that the percentage of false negatives would be too high to be useful. On the other hand at laparotomy, to take samples of ascitic fluid or to take peritoneal washings on all adnexal tumours for cytological studies is simple enough. To-date, experience at Johns Hopkins have shown that even in those apparently encapsulated tumours, free-floating intra-peritoneal cancer cells have been found thereby indicating possible microscopic peritoneal implants.

This is of extreme importance because it gives clinicians a tool in addition to clinical findings to determine the true extent of disease and institute adjuvant radio or chemotherapy or both, accordingly. Creasman and Rutledge (1971) further demonstrated that this simple procedure has prognostic value. His patients were divided into three groups:–

Group A: 98 patients with ovarian cancer had surgery as their primary treatment and of these 60% had Class IV and V cytology. The patients with normal cytology results have a much better survival rate than those with abnormal findings at one, two, three and four years.

Group B: 93 patients, previously treated, but having recurrent or persistent gross tumour, surprisingly had a lower percentage (48) of abnormal cytology.

Group C: 71 patients who had been treated with chemotherapy for various length of time were submitted to a "second-look" exploratory laparotomy. Twenty had no gross evidence of disease and of these 18 had normal cytology. The two who had abnormal cytology developed recurrence. Of the 51 who had disease either in the pelvis or abdomen only 53% had abnormal cytology and their prognosis was

worse than the patients with normal cytology specimen.

Why gross tumour sheds malignant cells in one patient and not in another patient is unknown. Still on the note of cytology. In this instance it concerns the peritoneal fluid cellular composition. McGowan and Davis (1970, 1972) observed that the female mouse is the laboratory model most comparable to women in this connection. They claim to be able to detect development of primary ovarian neoplasms by a significant change in the differential cellular patterns of peritoneal fluids. These observations occur months before morphological cellular changes appear in the peritoneal fluid. If similar correlation can be diagnostic aid for primary ovarian cancer in women.

Immunodiagnosis:

Tumourigenesis begins when one single cell, transforms itself through genetic alteration, gives rise a multiplicity of similarly altered cells. Such genetic change would induce the synthesis of a new protein, which in turn would be expected to provoke an immune response from the host. Proliferation of the malignancy would indicate failure of such immune response.

It should therefore be possible in theory at least, to diagnose ovarian or any cancer by identifying the specific antigen and/or antibody.

Levi (1971) using advanced ovarian lesions, and therefore with plentiful supply of altered protein, produced results to suggest the existence of a "specific" tumour antigen in papillary serous cystadenocarcinoma of the ovary. He went on to forecast that with refined radioimmuno-assay methods, it should be feasible to reveal nanogram amounts of antigen and thereby diagnosing ovarian cancer at its earliest stage.

If Levi's work is confirmed and can be applied clinically, it represents one of the few silver linings of the dark ovarian sky!

Clinical Staging:

Over the years many forms of staging have been used and none was free from deficiency. In the mid Sixties the International Federation of Gynaecology & Obstetrics (FIGO) adopted a method of clinical Staging (appendix I) and is universally accepted. However, even this does not take into account the significant prognostic difference between intact, completely encysted ovarian cancer; the surface exfoliating variety; and the cancer which has become exfoliating because the capsule has been ruptured or penetrated.

The "Second-look" operation:

In the first edition of Jeffcoate's Textbook of Gynaecology he cited an experience during his younger days when first appointed Consultant. There was a woman of 55 who presented for paracentesis every 3 months for 10 years after laparotomy had revealed an inoperable cancer of the ovary. He concluded that a 10 years history was incompatible with the diagnosis and recommended a second operation. This not only confirmed the diagnosis but also speeded the patient's demise.

Opinions have changed since then. Although radiation and chemotherapy are seldom curative, occasionally the clinical response may be sufficiently striking, – prolonged evidence of clinical remission, no abdominal masses no ascites and a freely mobile solitary tumour that was previously fixed – to warrant a repeat laparotomy. In addition, the "second-look" operation, in conjunction with peritoneal cytology, can be used to gain assurance of the disappearance of all tumour before stopping chemotherapy.

Chemotherapy:

As many ovarian cancers are not resectable or are incompletely resected at laparotomy, and adequate radiation rarely possible as disease has spread beyond the pelvis, it was inevitable that chemotherapy has been increasingly tried. In the nineteen fifties, less than 10% of ovarian cancers received this form of treatment. The figure increased to 30% in the sixties whereas to-day almost all receive some form of chemotherapy.

Chemotherapeutic agents act by having selective toxicity on the biochemistry of cancer cells, with different drugs acting on different phase of the cell cycle e.g. during DNA synthesis or during mitosis and so on. Unfortunately this toxicity also applies to vulnerable normal tissues thus accounting for the classical side effects. The major toxic effect which limits the use of chemotherapy is bone marrow suppression, and some of the advances to combat this include – transfussion of platelets or leucocytes prophylactic antibiotics, and reverse isolation. In reverse isolation the patient is protected from infection by a controlled flow of recirculating filtered air. The contaminated air brought

in by vistors is blown into filters and rendered bacteria-free before it is recirculated to her.

Many cytotoxic drugs have been and are still being assessed as to their efficacy. They may be used singly, like Endoxan, or Chlorambucil, both alkylating agents. Alternatively and increasingly more often recently, they are used in combination, involving in addition to an alkylating agent, an antimetabolite such as methotrexate or 5-fluouracil; an antibiotic like Actinomycin-D, plus an alkaloid like Vinblastine. Nitrogen mustard is usually reserved for effusions that fail to regress after systemic chemotherapy.

Although the presently available bewildering maze of data makes objective evaluation very difficult, there is general agreement that chemotherapy has a place in the management of ovarian cancer. The drugs definitely produce clinical improvement in many instances although they have yet to demonstrate significant effect on 5-year survival rates.

One typical report insa series of 130 patients gave this summary:— (Hreschyshyn 1966)

1. 17% show good response, i.e. 50% decrease in tumour size by palpation for 3 months.
2. 21% had "some" response.
3. in patients with ascites and/or pleural effusion, 26% had complete suppression of fluid and 38% partial suppression.
4. Patients with good response survive three times as long as those with no or poor response.
5. chemotherapy was the contributor to the death of 11 patients.

The last point raises many ethical problems of human experimentation in cancer therapy, as we are giving potentially lethal drugs. Voluntary consent is important and there should be a hospital committee to review study protocol. The overriding consideration is that the expected benefits should outweigh the estimated risks. This unfortunately is easier said than done.

Summary:

In summary this brief review attempts to highlight some of the current thinking and problems in ovarian cancer. Many investigations are continuing, and some with startling findings e.g.

1. It is now possible to culture various kinds of fresh ovarian cancer from human beings. (Rogers 1971).
2. A critical metabolic pathway is known for some tumours such as malignant papilloma of the rabbit, (Diddle 1971).

However, these and many others arebut small fragments of the big jig-saw puzzle the total picture of which is yet to emerge. An exciting field awaits the scientists and clinicians alike.

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Appendix I.

FIGO Staging of Carcinoma of the Ovary:

Stage	I	Tumor limited to one or both ovaries
	Ia	Tumor limited to one ovary
	Ib	Tumor in both ovaries
	Ic	Tumor in one or both ovaries, but with ascites in which tumor cells can be seen on cytologic investigation
Stage	II	Tumor in one or both ovaries with extension within the bony pelvis
	IIa	Extension and/or metastases to uterus and/or tubes
	IIb	Extension to other organs or tissue in the bony pelvis
Stage	III	Tumor in one or both ovaries with widespread intraperitoneal metastases involving the upper half of the abdominal cavity (including retroperitoneal glands and liver)
Stage	IV	Tumor in one or both ovaries with distant metastases outside the peritoneal cavity
Special category		Tumors that are thought to be cancer of the ovary, but in which surgical exploration has not been done so that certain classification is impossible.