PAPERS AND ORIGINALS

Histological Evidence of Tumour Rejection after Active Immunotherapy in Human Malignant Disease

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Summary

Active immunotherapy with multiple doses of tumour homogenate incorporated in complete Freund adjuvant was used to treat 12 patients with advanced malignant disease. Evidence of some tumour destruction was observed in 10. Improvement in general clinical condition and the disappearance of symptoms referable to tumour occurred in seven of the patients. The duration of improvement varied considerably. Histological evidence of lymphocytic infiltration, necrosis, and fibrous replacement of tumour tissue is presented.

Introduction

The immunological approach to cancer therapy has much theoretical background in its favour, but attempts to induce or augment immunological responsiveness against human tumours (Graham and Graham, 1959; Czajkowski *et al.*, 1967; Klein, 1969; Mathé, 1969) have been relatively unsuccessful. Tumour-bearing animals have been shown to mount a cellular immune response which is sometimes capable of tumour rejection (Foley, 1953; Klein *et al.*, 1960; Sjögren *et al.*, 1961). In man the evidence for immune cellular responsiveness directed against the specific antigens of some types of tumour is, though less direct, equally compelling (Southam *et al.*, 1966; Hellström *et al.*, 1968; Hellström and Hellström, 1969).

Considerable problems confront workers in this field. It is not ethical to treat by immunotherapy patients who might possibly be improved by conventional forms of therapy, yet by treating only the most advanced, "hopeless" cases the possibility of success is minimized. Not only may this form of therapy not help a patient but theoretically by immunological enhancement of tumour growth it is possible to increase the speed of tumour spread (Kaliss and Molomut, 1952; Kaliss, 1958; Gorer and Kaliss, 1959). The tendency has therefore been to treat only the most advanced disease, and hence poor results have been obtained. The evaluation of results is also difficult because of the great variation in tumour behaviour in different patients. Therefore any objective evidence of tumour destruction resulting from immunotherapy in advanced neoplastic disease would be encouraging. We report here a pilot study of active immunotherapy in advanced cancer, with histological evidence of tumour destruction.

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Materials and Methods

Twelve patients with advanced malignant disease were treated. All were considered by the referring surgeons to be unsuitable for any conventional form of cancer therapy. None had been treated by radiotherapy or chemotherapy. Details of the patients are given in the Table. In all cases the experimental nature of the proposed therapy was explained in detail to either the patient or a near relative. The extent of tumour growth was assessed by clinical examination and by other investigations where appropriate. All subjects were investigated for the presence of active

Details of Patients Treated and Response to Immunotherapy

Case No.	Age and Sex	Site and Type of Primary Tumour	Clinical Grading*	No. of Doses of Vaccine	Survival Time (Weeks)†	Clinical Response
1	F. 63	Ovary (carcinoma)	4	5	48 (D.)	Prolonged
2	M. 52	Rectum (carcinoma)	2	3	33 (D.)	Prolonged
3	M. 61	Stomach (carcinoma)	4	2	4 (D.)	Temporary
4	M. 58	Rectum (carcinoma)	2	3	7 (D.)	Uninfluenced
5	M. 38	Rectum (carcinoma)	2	6	87 (A.)	Prolonged
6	F. 62	Ovary (carcinoma)	3	3	9 (D.)	Temporary
7	M. 66	Stomach (carcinoma)	3	2	6 (D.)	Uninfluenced
8	F. 52	Perineum (melanoma)	1	5	27 (D.)	Prolonged
9	F. 48	Ovary (carcinoma)	3	5	47 (D.)	Prolonged
10	F. 21	Leg (melanoma)	1	2	68 (A.)	Prolonged
11	F. 60	Ovary (malignant clear cell tumour)	1	4	60 (A.)	Prolonged
12	M. 61	Stomach (carcinoma)	4	2	4 (D.)	Temporary

* Grade 1: Primary tumours excised but secondary deposits left in situ or primary tumour incompletely resected; no evidence of distant metastases. Grade 2: Metastatic deposits appeared some time after removal of primary tumour. Grade 3: Advanced primary tumours with spread to local tissues or regional lymph nodes or both; surgical removal considered impossible and only biopsy specimen removed. Grade 4: As grade 3 with, in addition, distant metastases.
† Survival time from start of immunotherapy to death or 31 October 1971. A = Alive. D. – Dead.

or latent tuberculosis. Samples of tumour tissue were obtained from metastatic deposits or from biopsy of primary tumours at laparotomy. A representative portion of each specimen was fixed in formalin for routine histological examination and the remainder used to prepare homogenates.

Under aseptic conditions tumour tissues were washed free of blood with cold physiological saline. They were trimmed as free as possible of fat, blood vessels, and fibrous tissue and chopped into small fragments. The fragments were homogenized in physiological saline in the proportion of 1 g of tissue in 10 ml of isotonic saline for 1 hour at 0-4°C in a Silverson tissue homogenizer at full power. After homogenization heavier debris was allowed to settle by gravity for 15 minutes and the supernatant collected. Two 1-ml aliquots of supernatant were tested for bacteriological sterility and the homogenate was subjected to freeze-thawing and then stored at −25°C.

For use as tumour vaccine the homogenate was emulsified with complete Freund adjuvant. The adjuvant consisted of commercially available incomplete Freund adjuvant (Difco) to which was added heat-killed human strain *Mycobacterium tuberculosis* 20 mg per 10 ml. Equal volumes of adjuvant and homogenate were freshly emulsified for each dose of vaccine. Vaccine was administered into the skin in the infraclavicular region. Two doses of 0·1 or 0·2 ml were given one into each side on several occasions. Doses were given at intervals of two to four weeks on two to six occasions (average number 3·5).

Patients were examined at frequent intervals during and after immunotherapy. Postimmunotherapy tumour tissue was obtained either by biopsy or at necropsy in several patients. This was examined by conventional histological methods and compared with tissue taken before immunotherapy.

Results

Clinical Observations.—Clinically observable changes took place in tumour tissue in many of the patients studied. Locally there was often an initial increase in size of the tumour mass associated with tenderness. The mass then usually became softer and sometimes fluctuant and this was later followed by diminution in size with a sharpening of the borders of the residual tissue. In the case of lymph node metastases these sometimes became impalpable. In general there was an increased sense of well-being, an improvement in appetite and weight gain, and often the disappearance of specific symptoms referable to the tumour. The clinical responses of the 12 patients are shown in the Table and are graded as (*a*) *uninfluenced* (two patients), where neither local changes in tumour nor improvement in general condition took place; (*b*) *temporary response* (three patients), in which there was clinical evidence of probable tumour destruction but the clinical course was little influenced; and (*c*) *prolonged response* (seven patients), in which the changes in tumour tissue and general condition took place and for a period of at least three months there was no evidence of progression of the disease.

Side Effects of Tumour Vaccine Therapy.—Ulceration of the injection sites occurred in all patients. This started 7 to 10 days after injection and reached a maximum size by the fourth week. The maximum size of the ulcerated areas varied from 1·5 to 3 cm in diameter and required 10 to 12 weeks for complete healing to occur. Surprisingly little discomfort was experienced, and slight intermittent itching and some tenderness were the only complaints. In most patients the axillary and sometimes the cervical lymph nodes became tender and enlarged after vaccine injections. The enlargement subsided within two to four weeks after the last dose of vaccine. All patients complained of an influenza-like illness starting from 6 to 36 hours after receiving the vaccine and lasting usually for 24 to 36 hours. The symptoms consisted of pyrexia, sweating, anorexia, occasionally nausea, and commonly muscular aching. Subsequent doses of vaccine tended to provoke more severe reactions, with similar symptoms which tended to start earlier and often required bed rest for 24 to 48 hours. Other than the changes observed in tumour tissue described above no evidence was found of vaccine effects elsewhere.

Histological Findings.—From six of the 12 patients it was possible to obtain tumour tissue after immunotherapy for comparison with that taken previously. Three of these specimens were obtained by biopsy and the remaining three at necropsy. The case histories of these six patients are presented below.

CASE 1

A 63-year-old woman was found at laparotomy to have a large papillary adenocarcinoma of the ovary with metastatic deposits in the bowel wall and mesentery. It was considered to be surgically impossible to remove the main tumour mass. She was treated with five spaced doses of tumour vaccine. Reduction in size of the palpable mass occurred, with improvement in general condition and in both intestinal obstruction and difficulty with micturition. Biopsy of an enlarged inguinal lymph node taken eight months after immunotherapy was started showed partial replacement of the node by tumour and no clear evidence suggestive of tumour rejection. She died 48 weeks after the start of immunotherapy. Necropsy was not performed.

CASE 2

Fourteen months after abdominoperineal resection of carcinoma of the rectum (Fig. 1) a 52-year-old man presented with enlarged right inguinal and bilateral cervical lymph nodes. He was treated with three doses of tumour vaccine spaced at four-weekly intervals. After the first dose the nodes became swollen and tender but subsequently

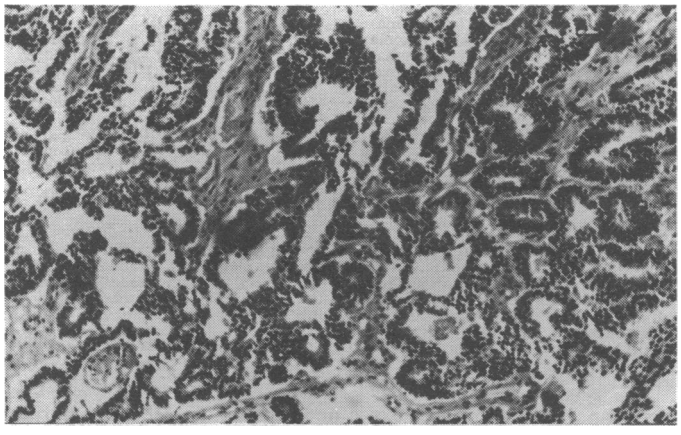

FIG. 1—Case 2, preimmunotherapy specimen. Primary adenocarcinoma of rectum. (H. and E. ×78.)

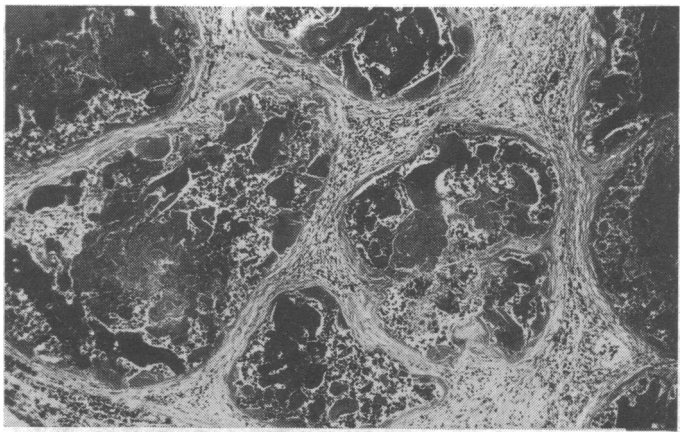

FIG. 2—Case 2, postimmunotherapy. Para-aortic lymph node metastasis. Specimen shows necrosis of tumour cell deposits with encircling fibrous tissue. (H. and E. ×31·2.)

decreased in size and became more discrete. Two months later the cervical nodes had become impalpable and the inguinal nodes fluctuant. He remained well and returned to work for a short time, but by the fourth month he developed troublesome lymphoedema of the penis, scrotum, and later of the legs. Subcutaneous metastatic deposits were found in the inguinal region. He developed acute pyelonephritis and died 33 weeks after the treatment started.

At necropsy there were multiple secondary deposits of tumour in the liver. Many enlarged lymph nodes were found, all of which were almost entirely replaced by "caseous" material. Microscopically the necrosis of tumour within lymph nodes was confirmed. No acid-fast bacteria could be found on appropriate staining, and culture of the caseous material was sterile. Few, if any, tumour cells could be found in the nodes. The appearances of a lymph node section are shown in Fig. 2. Many of the liver metastases were frankly necrotic, while some appeared to have a peripheral zone of fibrous tissue. Histological examination confirmed the naked-eye appearances. The centres of the metastases were necrotic and were surrounded by a zone of fibrous tissue in which islands of tumour cells, mostly appearing degenerate, were found (Fig. 3). At the periphery of the metastases adjacent to the liver tissue was a narrow zone containing many lymphocytes and occasional tumour cells (Fig. 4). Nowhere was active invasion of the liver substance by tumour cells seen.

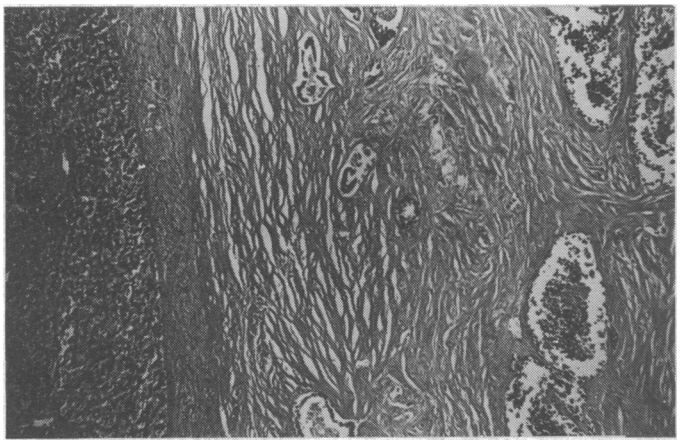

FIG. 3—Case 2, postimmunotherapy. Hepatic metastasis. Specimen shows fibrous replacement of periphery of tumour deposit with islands of tumour cells, many of which appear necrotic. (H. and E. ×31.)

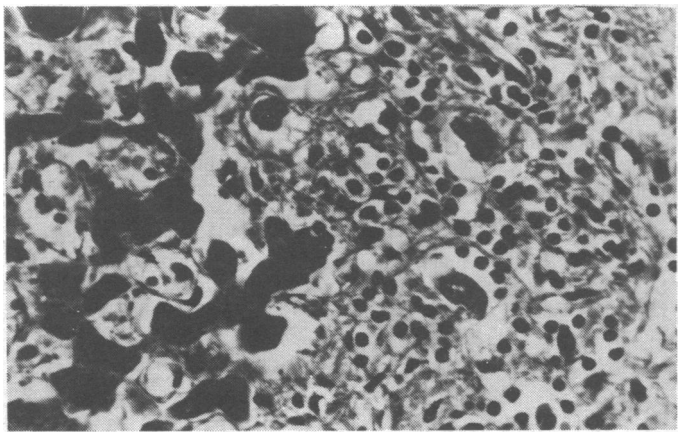

FIG. 4—Case 2, postimmunotherapy. Periphery of hepatic metastasis shows infiltration with lymphoid cells. Two tumour cells are present in the midst of infiltrating lymphoid cells. (H. and E. ×312.)

CASE 3

Five months after total gastrectomy for carcinoma of the stomach this 61-year-old man developed dysphagia and a hard nodule in the abdominal scar. The nodule gradually increased in size and ulcerated. The histological appearances of a biopsy specimen of the nodule are shown in Fig. 5. His dysphagia became more severe and was treated by dilatation. He was given two doses of tumour vaccine. The ulcerated nodule began to heal after one dose and oesophageal bougienage became easier to carry out. He died with intractable vomiting four weeks after the start of immunotherapy.

Necropsy showed that in addition to the subcutaneous secondary deposit in the abdominal scar there were metastases in the left adrenal and tumour tissue was present around the lower end of oesophagus and in the region of the pancreas. Even in the peripheral portion of the subcutaneous metastasis distant from the ulcerated area much of the tumour tissue was necrotic. Part of the deposit was replaced by fibrous tissue in which were small islands of tumour cells surrounded by a zone of lymphocytes (Figs. 6 and 7). Widespread necrosis of tumour was found in relation to both the lower end of the oesophagus and the pancreas. Again, surviving islands of tumour cells were infiltrated with lymphocytes. The appearance of tumour in the region of the pancreas is shown in Fig. 8.

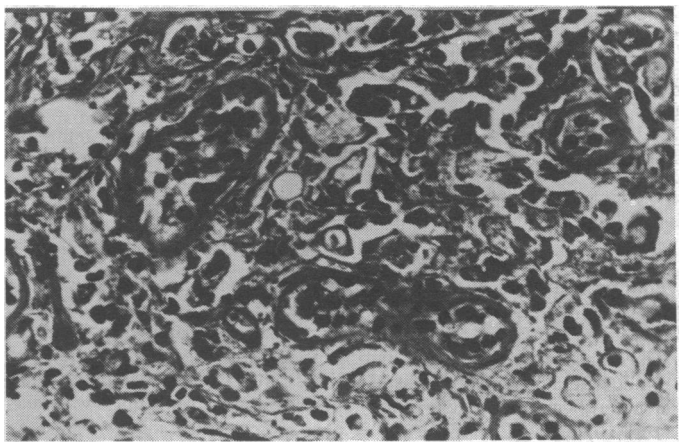

FIG. 5—Case 3, preimmunotherapy. Biopsy specimen of subcutaneous metastasis from carcinoma of stomach. (H. and E. ×312.)

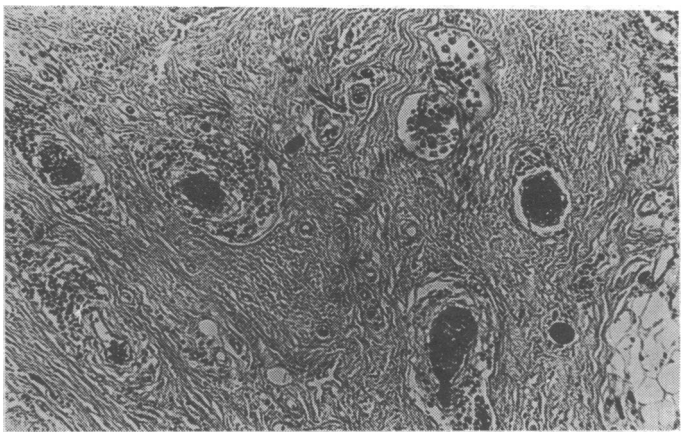

FIG. 6—Case 3, postimmunotherapy. Peripheral portion of subcutaneous metastasis showing fibrous replacement with islands of tumour cells surrounded by lymphoid cells. (H. and E. ×78.)

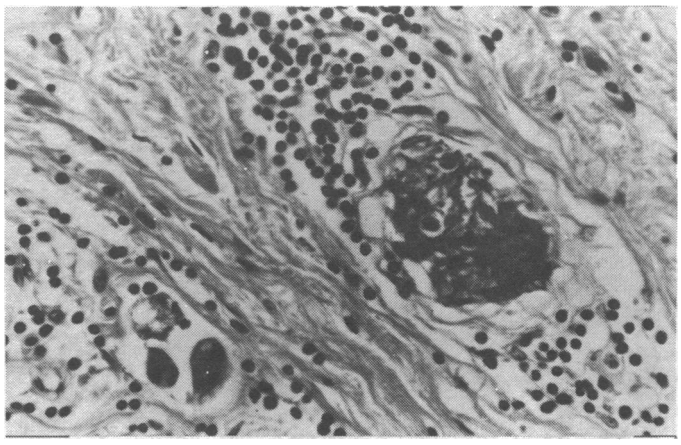

FIG. 7—Case 3, postimmunotherapy. Subcutaneous metastatic deposit. Islands of necrotic tumour cells surrounded by dense lymphocytic infiltration. (H. and E. ×312.)

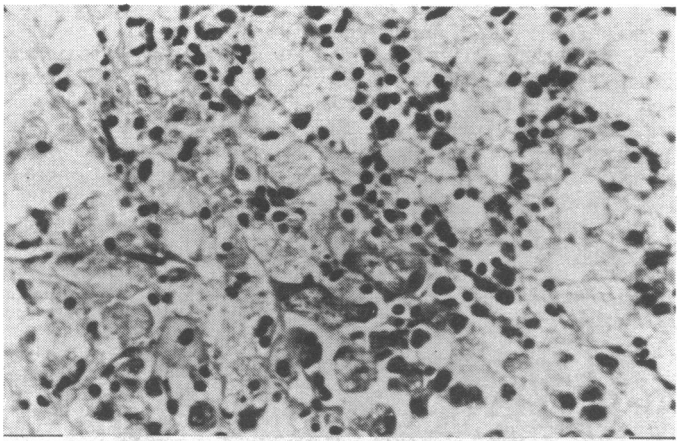

FIG. 8—Case 3, postimmunotherapy. Tumour tissue from bed of stomach showing extensive tumour cell necrosis with "ghost cells" and infiltration with lymphoid cells. (H. and E. ×312.)

CASE 5

Four years after an anterior resection for adenocarcinoma of the rectum (Fig. 9) this 38-year-old man presented with abdominal pain, weight loss, anorexia and nausea, and constipation. Laparotomy showed large malignant para-aortic lymph nodes and the pelvic cavity contained much malignant tissue. The sigmoid colon, which was obstructed, was freed and a biopsy specimen of a lymph node was taken (Fig. 10).

He was treated with four spaced doses of tumour vaccine. His appetite improved and his weight increased and for a period he became free of symptoms and signs. Eight months after the start of immunotherapy he developed dyspeptic symptoms and was found to be anaemic. His blood urea was 230 mg/100 ml, and retrograde pyelography showed bilateral hydronephrosis with an S-form distortion of the right ureter at the level of the pelvic brim. Laparotomy and exploration of both ureters one year after the start of immunotherapy showed that the tumour previously present in the pelvis was no longer detectable. There was no evidence of recurrence of tumour in the colon or rectum or at the site of anastomosis and the liver was free of metastases. Both ureters were distorted and obstructed by hard masses of fibrous tissue where previously there had been malignant para-aortic lymph nodes. The ureters were easily freed from the hard tissue, which on histological examination showed a few small collections of undifferentiated tumour cells embedded in dense fibrous tissue (Fig. 11). After the operation his blood urea fell and his haemoglobin returned to normal. He remained well.

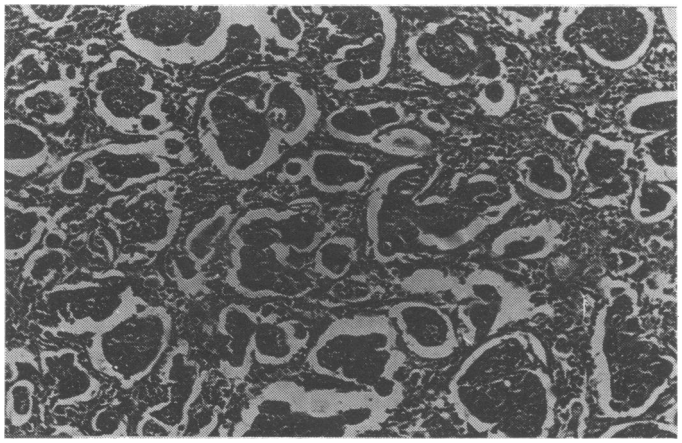

FIG. 9—Case 5, preimmunotherapy. Primary adenocarcinoma of rectum. (H. and E. ×78.)

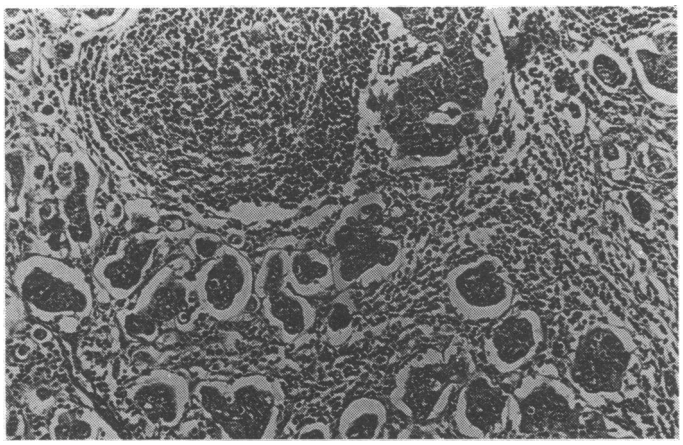

FIG. 10—Case 5, preimmunotherapy. Biopsy specimen from para-aortic lymph node showing cortical metastatic deposits. (H. and E. ×78.)

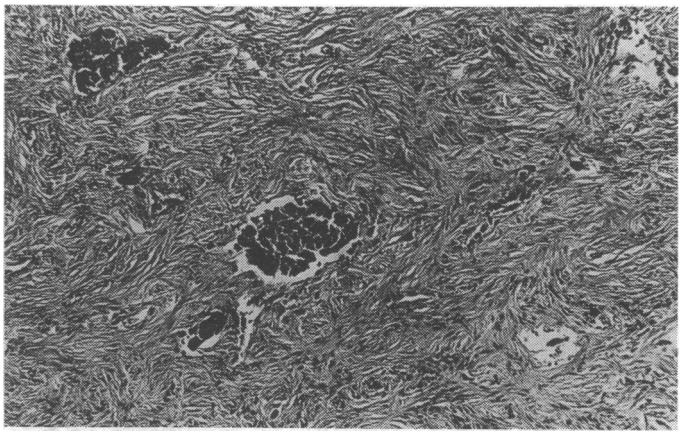

FIG. 11—Case 5, postimmunotherapy. Biopsy specimen from tissue replacing malignant para-aortic lymph nodes showing dense fibrous tissue with small islands of tumour cells. (H. and E. ×78.)

CASE 8

This 52-year-old woman developed a malignant melanoma near the anus which was removed in June 1968. A local recurrence was removed 20 months later, but within a month she developed a further recurrence, which ulcerated. Biopsy of an enlarged inguinal lymph node showed metastasis. She was treated with five spaced doses of tumour vaccine. After the first two doses the perineal ulcer healed rapidly and completely. At the same time, however, a small pigmented lesion in the natal cleft increased in size and became pedunculated. A mass developed in the left ischiorectal fossa which was explored. This proved to be a lobulated metastasis about 6 cm in diameter. A portion of the mass was removed but the major part was left in situ. Histologically the tissue showed some lymphocytic infiltration but no clear evidence of tumour destruction. Three weeks after partial removal of the tumour mass the remaining tumour tissue regressed completely. By 11 weeks after the start of immunotherapy she developed metastatic deposits in the labia majora and in both inguinal lymph node groups. She died 27 weeks after the start of immunotherapy. Necropsy was not carried out.

CASE 9

An obese 48-year-old diabetic woman was found at laparotomy to have a large malignant tumour arising in the left ovary invading the posterior abdominal wall and the region of the sigmoid colon. Metastatic deposits were present in the peritoneum and liver. Biopsy of the tumour showed a papillary adenocarcinoma of the ovary (Fig. 12). She was treated with five spaced doses of tumour vaccine. Over the ensuing four months the mass gradually became smaller, more discrete, and more mobile. Five months after starting immunotherapy she developed two small nodules in the laparotomy scar. Biopsy of these showed them to be metastatic tumour. She remained in reasonable health until 11 months after the start of immunotherapy, when she was admitted to hospital with hypoglycaemia. She developed an inferior vena caval thrombosis and died.

At necropsy most of the primary tumour was found to be necrotic. Metastatic deposits were found in the liver and lymph nodes. There

was bilateral hydronephrosis and a severe urinary tract infection. Histologically extensive necrosis of tumour, both primary and secondary, was confirmed. The appearances of a liver metastasis were very similar to those described in Case 2. The periphery of the deposit was replaced by a zone of fibrous tissue which was infiltrated with lymphocytes (Fig. 13). Inside the fibrous zone was tumour, part of which was necrotic. Active invasion of the liver by tumour cells was not seen.

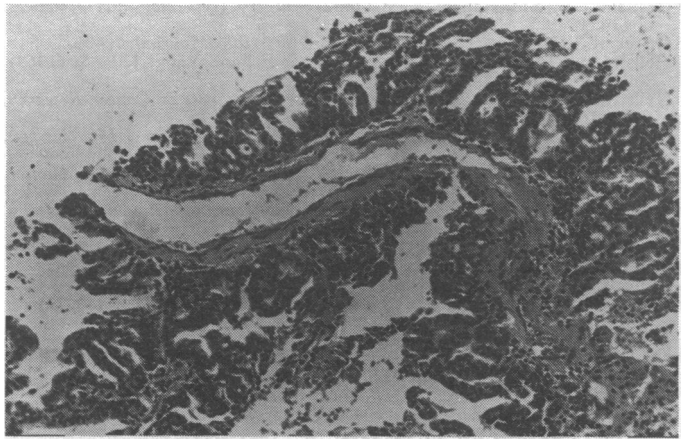

FIG. 12—Case 9, preimmunotherapy. Primary papillary carcinoma of ovary. (H. and E. ×78.)

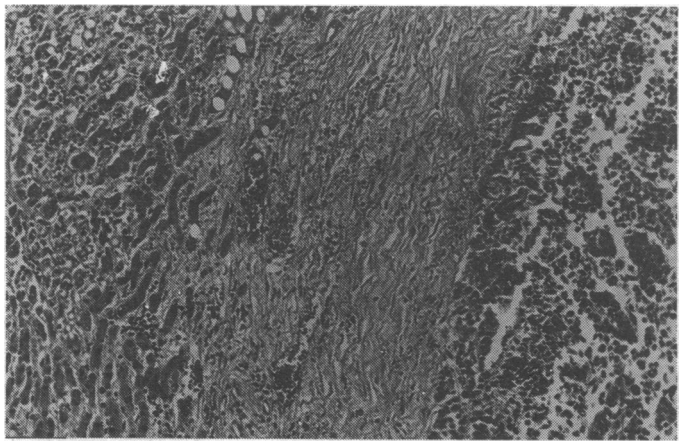

FIG. 13—Case 9, postimmunotherapy. Liver metastasis showing peripheral replacement by fibrous tissue containing occasional tumour cells and infiltrated by lymphocytes. (H. and E. ×31.)

Discussion

A number of different immunological approaches have been used in attempts to destroy tumour cells in vivo in man. Non-specific stimulation of the reticuloendothelial system with a variety of agents that have produced a slowing of tumour growth in animals (Old *et al.*, 1961; Woodruff and Boak, 1966) has also been tried in man. Repeated B.C.G. vaccination of leukaemic patients in remission was used by Mathé (1970) and produced some prolongation of remission. *Bordetella pertussis* vaccine has also been used in a similar context with only very slight prolongation of the time of remission (Guyer and Crowther, 1969). Lymphocytes, either from normal donors (Woodruff and Nolan, 1963) or from specifically sensitized individuals (Nadler and Moore, 1966), have been injected into patients with malignant disease. The results suggest some temporary beneficial effect in some patients. More recently attempts to induce specific tumour rejection by the use of transfer factor derived from the leucocytes of specifically sensitized individuals have produced reduction in tumour size with improvement in clinical condition (Brandes *et al.*, 1971). There have been several attempts to use antisera to treat advanced human malignant disease (Murray, 1958; Finney *et al.*, 1960). While some beneficial effects were claimed the possibility of immunological enhancement should now deter workers from this approach.

Attempts to induce or increase immunological reactivity against human tumours by immunization with autologous tumour preparations have been made intermittently. In general the clinical results have been disappointing. Tumour extracts and cells without adjuvants were used by Kellock *et al.* (1922), Murray (1958), Ikonopisov *et al.* (1970), and Currie *et al*, (1971) with little or no influence on the course of the disease. Freund-type adjuvants in combination with tumour homogenates were used by Graham and Graham (1959, 1962), Finney *et al.* (1960), and Pruit *et al.* (1963). The last two groups of workers did not state whether the Freund adjuvant used was of the complete or incomplete type, but Graham and Graham used both varieties. The only evidence of possible clinical benefit was presented in the series of 371 patients treated by Graham and Graham (1962). After surgical treatment 232 of these patients were given immunotherapy followed by radiotherapy and the remaining 139 were treated by radiotherapy or chemotherapy. The two-year survival rate was "rather better" in the immunotherapy group, and it was believed that provided a large proportion of the tumour mass had been removed surgically immunotherapy potentiated the effects of radiotherapy.

By using B.C.G. in combination with irradiated leukaemic cells Mathé (1970) induced significant prolongation of remission in leukaemic patients. The remissions were first induced by chemotherapy. These results are rather more convincing than those of any other immunotherapeutic approach to malignant disease. The reason may well be that in remission the leukaemic patient is carrying a much smaller load of malignant cells than most patients with solid tumours. When all the reported series are considered in which immunization was with an autologous tumour preparation rather better clinical results were obtained in those in which adjuvants, particularly mycobacterial adjuvants, were used. Even so, objective evidence of tumour destruction is very sparse.

The overall clinical results obtained in our small series are similar to those of Graham and Graham (1959, 1962). Although only three of the 12 patients were alive at the time of writing there was some clinical evidence of tumour destruction in 10 patients, and in seven it was considered that worth-while clinical improvement associated with evidence of tumour destruction took place. It was noted that improvement in clinical condition tended to occur after each dose of vaccine, and that some deterioration might later occur but further improvement would follow additional doses. The same observation applied to clinical evidence of tumour destruction. It appeared to take place in responding patients for a period of time after each dose. It is, however, impossible to reach firm conclusions on clinically observed changes in so variable a disease process as advanced malignant disease. Not only is the clinical course of malignant disease very variable but so is the response of the patient to immunotherapy. Thus only a very large controlled clinical trial could possibly prove the clinical efficacy of immunotherapy.

The histological evidence presented shows convincing changes in tumour tissue after immunotherapy. The changes observed in four out of six patients of tumour cell necrosis with heavy lymphocyte infiltration and fibrous replacement of tumour suggest that immunotherapy with tumour homogenates incorporated in complete Freund adjuvant is able to induce some measure of tumour rejection. Although there is a remote possibility that the tumour rejection observed was not related to the immunotherapy it is very unlikely. In all patients it was possible to find surviving tumour cells. Thus in advanced disease, while reducing the "tumour load" in some patients immunotherapy does not result in cure. Is it therefore worth while?

Temporary improvement in clinical condition occurred in most of the patients. In some (Cases 5, 10, and 11) this improvement was maintained for a sufficiently long period of time and allowed a sufficiently high quality of life to be without doubt of value to the patient. The side effects of immunotherapy proved to be acceptable to the patients and to last for only a limited time. Evidence of enhancement of tumour growth was not seen.

Thus in the context of advanced neoplastic disease immunotherapy carried out by the method described provides a form of palliation for some patients. It does not offer a cure in these patients. Whether this method would improve the survival rate by killing all tumour cells in patients with only a small residual tumour load after surgery remains to be decided. Other aspects require investigation. What are the mechanisms of the tumour rejection observed? Is there an increase in the number of cytotoxic lymphocytes, is blocking factor (Hellström and Hellström, 1970a) reduced, are unblocking factors (Hellström and Hellström, 1970b; Bansal and Sjögren, 1971) produced? With a greater understanding of the mechanisms involved it might prove possible to design a more effective immunotherapeutic regimen by altering the constitution, frequency, and number of doses of vaccine. It might also prove possible to determine which patients are likely to derive most benefit from immunotherapy. It is, however, very unlikely that immunotherapy will ever replace other, conventional forms of therapy but it could become a useful adjunct to surgery, radiotherapy, and chemotherapy.

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Oral Prostaglandins in the Induction of Labour

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Summary

Prostaglandins E_2 and $F_2\alpha$ were administered by mouth to induce labour in 24 patients at or past term. The drugs were administered at two-hourly intervals in doses ranging from 0·5 to 1·5 mg for prostaglandin E_2 and from 5 to 15 mg for prostaglandin $F_2\alpha$. Of the 10 cases in which prostaglandin E_2 was used, labour was successfully induced in eight and there were no side effects. With prostaglandin $F_2\alpha$ labour was induced in 12 of 14 patients nine of whom had gastrointestinal disturbance, mostly of mild degree. With both drugs the infant was apparently unaffected and Apgar scores were satisfactory. Uterine hypertonus was not observed and the postpartum blood loss was within normal limits.

Introduction

Recent clinical trials with prostaglandins E_2 and $F_2\alpha$ have established their efficacy in inducing labour when administered by continuous intravenous infusion (Karim *et al.*, 1968, 1970; Beazley *et al.*, 1970; Embrey, 1970; Karim, 1970.) It has also been reported (Karim, 1971; Karim and Sharma, 1971) that these drugs are effective when given by mouth, but the available evidence is scanty and there is as yet no published work on the subject from the Western hemisphere. The present study is of a preliminary trial of the action of both these prostaglandins in the induction of labour when administered by the oral route and reports the results obtained in 24 patients who were studied in detail.

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Patients and Materials

Twenty-four patients were included in the series, of whom 10 were treated with prostaglandin E_2 and 14 with $F_2\alpha$. All were at or past term, and the reasons for induction are listed in Table II (E_2) and Table III ($F_2\alpha$). Ages ranged from 21 to 37 years, and all, with the exception of one primigravida, were healthy parous patients whose membranes were intact at the onset of treatment. In all cases the "inducibility" rating of the patient was assessed by the method of Bishop (1964) (see Table I) and

TABLE I—*Inducibility Rating—Bishop's (1964) Method*

Factor	Score 0	Score 1	Score 2	Score 3	Factor Score*
Dilatation (cm)	Closed	1–2	3–4	5 or more	0–3
Effacement ..	0–30%	40–50%	60–70%	80 % or more	0–3
Station ..	—3	—2	—1,0	+1, +2	0–3
Consistency ..	Firm	Medium	Soft	—	0–2
Position ..	Posterior	Mid	Anterior	—	0–2
				Total score	0–13

*0–5 = unfavourable, 6–13 = favourable.