caesarean section and the other a gravida-5 who had a puerperal sterilization performed—subsequently became pregnant. The first patient had a bilateral salpingectomy performed at repeat caesarean section and the second a repeat Pomeroy ligation three months after delivery.

When the 70 patients who required hysterectomy subsequent to sterilization were looked at separately it was noted that 50 of them were gravida-5 or more, 15 had been subjected to repeat caesarean section and sterilization, and three were sterilized at the time of hysterotomy. Of the 22 patients requiring repair of prolapse 20 had had four or more confinements.

Discussion

The findings in this study confirm those of others that there is a relatively high incidence of subsequent pelvic disease in patients subjected to tubal ligation. The incidence of subsequent gynaecological consultation and treatment in this study was 43%. A total of 95 patients (25%) required further major gynaecological surgery. The commonest symptom was menstrual disturbance, and more than 90 patients were treated for this, 49 requiring hysterectomy for control. Williams et al. (1951) suggested primary hysterectomy as the treatment of choice in all patients desiring or requiring sterilization, but it is felt that this is too major a procedure for every patient. This study shows that most patients requiring further major surgery were either highly multiparous or had had surgical wounds in the uterus either at caesarean section or hysterotomy.

The fact that there is a relatively high incidence of subsequent hysterectomy in patients having caesarean sections has already been noted. Weeds (1959) found that 14% of his patients who had had a caesarean section ultimately came to hysterectomy, and several American authors (Montague, 1959; Pletsch and Sandberg, 1963) have suggested that patients who have been subjected to several caesarean sections and who wish to

be sterilized should have elective caesarean hysterectomy at delivery in their last pregnancy. Owing to the high incidence of complications, such as bladder injury and postoperative haematoma formation following the operation, this is unlikely to be adopted in this country. It would seem reasonable, however, in highly parous patients requesting or requiring sterilization to take a careful menstrual history, and those who have had previous menstrual disorders even before a present pregnancy might well be better treated by hysterectomy, if necessary delaying operation until complete involution of the pelvic organs has taken place. If there is evidence of prolapse vaginal hysterectomy and repair, where feasible, would seem to be the procedure of choice. The occurrence of five cases of cervical carcinoma (three of these lesions in situ) emphasizes the importance of checking cervical cytology before operation.

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PRELIMINARY COMMUNICATIONS

Carcinoembryonic Antigen in Faeces

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Summary

Carcinoembryonic antigen (C.E.A.) was detected in the faeces of 5 out of 10 healthy volunteers, 12 out of 18 patients suffering from gastrointestinal cancer (including 10 out of 11 cases of colonic cancer), and 3 out of 13 patients suffering from non-neoplastic disease. It is suggested that C.E.A. may be present in small amounts in normal faeces but that in malignant conditions of the bowel the amount increases.

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Introduction

Carcinoembryonic antigen (C.E.A.) is the name given by Gold and Freedman to a protein-polysaccharide complex of sedimentation coefficient 6·9 to 8·0 S which is present in epithelial cell membranes of fetal gastrointestinal structures, disappears at about six months' gestation, and in the adult is found in adenocarcinomata of the gastrointestinal tract (Gold and Freedman, 1964, 1965; Krupey et al., 1968; Gold et al., 1968). The demonstration by Thomson et al. (1969), using a radio-immunoassay technique, of circulating C.E.A. in the serum of 35 out of 36 patients with colonic or rectal cancer but not in sera from patients with a wide variety of other complaints suggested that the method might be used as a diagnostic test for bowel cancer. In the hands of Moore et al. (1971), however, the test appeared to be less specific. Though they confirmed the finding of circulating C.E.A. in patients with colonic cancer the test was also positive in several cases of lung cancer, alcoholic liver disease, and uraemia, and Lo Gerfo et al. (1971), while again confirming the results of Thomson et al. (1969) with respect to colonic cancer, also found circulating C.E.A. in a few cases of non-neoplastic bowel and lung disease as well as cancers of the breast, ovary, uterus, bladder, prostate, and kidney.

Since the turnover of epithelial cells in the intestine is so high it seemed logical to look for C.E.A. in the faeces of patients with gastrointestinal cancer, where C.E.A. of extra-alimentary origin would be unlikely to be present.

Materials and Methods

Specimens of cancerous bowel were obtained fresh from the operating theatre. Blocks of tissue were fixed for conventional histological examination. From most specimens a piece of normal bowel mucosa from at least 7 cm from the margin of the tumour was obtained to act as control, as used by Gold and Freedman (1964). Specimens of faeces were obtained from patients with bowel cancer, patients with a variety of other conditions, and healthy volunteers. Human embryos were obtained fresh from therapeutic abortions. All types of specimen were either processed immediately by the method of Krupey et al. (1968) or stored at —20°C until needed.

Tissue specimens were washed with distilled water and cut into small pieces with scalpel and scissors. When processing normal mucosa small amounts of submucosa and muscle coat from the same section of bowel were included. Specimens were then homogenized in distilled water by using a Silverson Sealed Unit Mixer at maximum speed for a sufficient length of time to disrupt most of the cells (one hour for the adult and fetal tissues, 15 minutes for the faeces). The container was immersed in melting ice throughout.

The homogenates were then mixed with an equal volume of 1·2M perchloric acid, stirred at room temperature for 30 minutes, then centrifuged at 20,000 g for one hour at 5°C. The supernatants were dialysed against running tap-water for 48 hours, centrifuged again under the same conditions, and the supernatants dialysed against distilled water at 4°C for 24-48 hours. The non-dialysable material was then freeze-dried, weighed, and redissolved in distilled water to a concentration of 10 mg/ml for the solid tissues and 25 mg/ml for the faeces.

Antisera were raised in rabbits by using freeze-dried tumour extracts in complete Freund's adjuvant. Seven spaced doses were given in all. The best serum was absorbed with a pool of freeze-dried extracts of seven samples of normal bowel and also with freeze-dried stromata from lysed washed human AB red blood cells. Absorption was continued until the antiserum produced no lines of precipitation on gel immuno-diffusion against either extract of normal bowel or normal human serum and no agglutination occurred with washed human AB red blood cells. Extracts were tested against this absorbed antiserum by double diffusion in 1% agar gel at pH 7·3.

The specificity of the reaction was investigated by further absorption of the absorbed antiserum with extracts which gave positive reactions. This reabsorbed serum was then retested against other "positive" extracts.

Results

The unabsorbed rabbit antiserum gave multiple lines on gel immunodiffusion against both neoplastic and normal tissue extracts as well as against normal human serum. It also agglutinated washed human AB red blood cells. Ten serial absorptions with extracts of normal tissue were required before all anti-normal activity disappeared. One absorption with washed freeze-dried human AB red cell stromata was enough to remove anti-red-cell activity. When completely absorbed the serum produced a single line on gel immunodiffusion against extracts of 17 out of 18 tumour tissues but against only 1 out of 11 normal tissues. This extract was shown by precipitation inhibition to contain the same antigen as that demonstrated in tumour tissue.

Reactions of identity were invariably observed between adjacent lines irrespective of the source of the antigen (see Fig.). One batch of this absorbed antiserum was tested against all extracts of tissue and faeces. The results are summarized in the Table. It will be seen that all six extracts of fetal intestine contained detectable C.E.A.

Faeces from 10 of the 11 patients with colonic cancer contained detectable C.E.A. The only exception was in the case of a patient whose tumour was itself negative. Two out of three

Results of Testing and Faeces for Presence of Carcinoembryonic Antigen

	No.	Positive	Negative
Tissues:			
Alimentary cancer	18	17	1
Normal bowel	11	1	10
Fetal bowel	6	6	0
Other gastrointestinal disease	2	1*	1
Faeces taken from area distal to cancer of the:			
Caecum, colon, and rectum	11	10	1
Pancreas and common bile duct	3	2	1
Stomach	3	0	3
Oesophagus	1	0	1
Faeces taken from area proximal to cancer of the colon	3	0	3
Faeces after resection of colonic cancer	3	0	3
Faeces after other alimentary disease	11	3†	8
Faeces after non-alimentary disease	2	0	2
Faeces after healthy volunteers	10	5	5

*Endometriosis of the colon.
†1 ? Crohn's disease, 1 diverticulitis, 1 "multiple peritoneal adhesions."
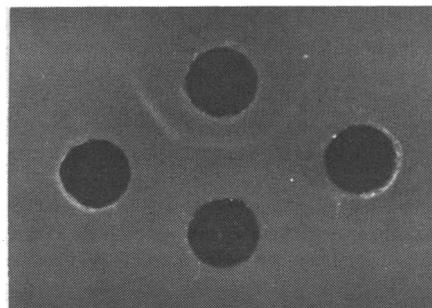
Double diffusion in gel to show reaction of identity of C.E.A. in carcinoma of colon (lower central well), fetal gut (right well), and faeces from patient with carcinoma of colon (left well). The anti-C.E.A. is in the upper well.

faecal specimens from patients with biliary and pancreatic cancer were positive. All three faecal specimens from patients with stomach cancer were negative, as was the one specimen of faeces from a case of oesphageal cancer. In three patients faeces were obtained from proximal to the cancer via a colostomy; all were negative. On three occasions post-resection specimens of faeces were tested; all were negative.

Three out of 13 patients suffering from non-neoplastic disease were found to have demonstrable faecal C.E.A. as were 5 out of 10 healthy volunteers.

All these positive results gave reactions of identity with extracts of colonic cancer. Absorption of aliquots of the anti-C.E.A. with each of these faecal extracts completely removed reactivity against extracts of colonic carcinoma.

Discussion

The findings relating to the normal, malignant, and fetal tissues confirm those of Gold and Freedman (1965), Kronman and Localio (1970), and Burtin and von Kleist (1970). The finding of C.E.A. in one specimen of endometriosis and one of normal bowel, however, would seem to support those of Martin and Martin (1970), who found a substance which appeared to be identical with C.E.A. in several normal alimentary tissues though in much lower concentrations than in alimentary cancers. The suggestion arising from their work is that the difference between normal and neoplastic colon with respect to C.E.A. is quantitative and not qualitative.

This suggestion is further borne out by the finding of C.E.A. in faeces from 5 out of 10 healthy volunteers but in 10 out of 11 patients with colonic cancer. The gel-immunodiffusion method is relatively insensitive, and it is possible that if a more sensitive technique were used C.E.A. would be found routinely, though in lower concentrations, in the faeces of healthy individuals.

There is a faint possibility that the five healthy volunteers in whose faeces we found C.E.A. were in fact suffering from cancer or possibly polyposis coli or else that their alimentary canals contained rests of fetal epithelium. We regard these

suggestions as highly unlikely and investigations are being undertaken to exclude them. It is also possible that the three patients suffering from non-neoplastic bowel disease were carrying occult cancers. They are being kept under surveillance.

The lower proportion of positive faeces in patients whose cancers were proximal to the large bowel bears out the findings of Gold and Freedman (1956) that the concentration of C.E.A. in alimentary cancers diminishes from below upwards.

It is clearly of the first importance to apply a quantitative technique to the demonstration of C.E.A. in faeces. It may be possible to define "normal limits" of faecal C.E.A. in the healthy population above which a diagnosis of alimentary carcinoma should be considered. This question is receiving attention. It remains to be seen whether serum or faeces is the best material to examine with a view to designing a diagnostic test.

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MEDICAL MEMORANDA

Factitious Hypoglycaemia: Chlorpropamide Self-administration by a Non-diabetic

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Factitious hypoglycaemia produced by using insulin or sulphonylureas classically occurs in women aged between 20 and 40 who either themselves have used insulin or oral antidiabetic agents or have relatives who are diabetics or are employed in a medical or paramedical capacity (Creutzfeldt and Frerichs, 1969). We add here a further report to the few published cases of factitious hypoglycaemia due to oral antidiabetic drugs (Duncan, Jenson, and Eberly, 1961; Gittler, 1962; Creutzfeldt and Frerichs, 1969).

Case Report

A married woman, a trained nurse aged 30, was investigated because of occipital headaches for 13 years, periodic episodes of unconsciousness for four months, and glycosuria. Her father and both parental grandparents had diabetes mellitus. She had had intermittent glycosuria since childhood but random blood sugars were normal. The headaches had worsened and for the past four months had been accompanied by nausea, vomiting, and, on about six occasions, "blackouts" preceded by sweating and double vision. She attended three hospitals in succession. Haematological investigations and x-ray examination of the chest and skull at the first hospital showed nothing abnormal. An oral glucose tolerance test gave a fasting glucose of 118 mg/100 ml, 113 at 30 min, 104 at 60 min (urine sugar 7·5 g/100 ml), 84 at 90 min, 75 at 120 min (urine sugar 10 g/100 ml), and 50 at 150 min. The blood glucose was

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52 mg/100 ml. An intravenous glucagon test showed fasting blood glucose of 75, 95, and 172 mg/100 ml. After glucagon (1 mg) blood sugars were 219 mg/100 ml at 5 min, 234 at 10 min, 247 at 15 min, 252 at 30 min, 171 at 60 min, and 132 at 120 min. Blood insulin values were reported as normal. Attacks of faintness were treated successfully with intravenous glucose.

On admission to the second hospital for neurological investigation the patient had a "funny turn" two hours after the evening meal. The blood sugar was 24 mg/100 ml, and during the next three days blood glucose levels were 22, 10, 35, and 10 mg/100 ml and she was unrousable on two occasions. Continuous infusion of 5% glucose was started but she again became hypoglycaemic. She was then transferred to the third hospital. No abnormalities were found on physical examination. The blood glucose was 270 mg/100 ml; plasma electrolytes, calcium, liver function tests, E.C.G., and x-ray pictures were normal; plasma cortisol was 22 μg/100 ml (11 a.m.). She was maintained on 5% glucose intravenously (500 ml/three hours) for two days. The infusion was stopped at 11 a.m. when the blood glucose was 105 mg/100 ml. Tolbutamide 1 g was given intravenously at 1 p.m., when the blood glucose was 80 mg/100 ml. The blood glucose fell to 55 mg/100 ml at 106 min but then rose again (see Table). Despite a further 22 hours of starvation

Blood Glucose and Serum Insulin* Values

Date	Time	Blood Glucose (mg/100 ml)	Serum Insulin (μU/ml)	Notes
27/6	11.30 a.m.	270	66	On 5% glucose I.V.
	6.40 p.m.	80	49	,,
28/6	9.00 a.m.	90	39	,,
	8.00 p.m.	200	35	,,
29/6	11.00 a.m.	105	15	,,
	Noon	85	6	
	1.00 p.m.	80	7	I.V. tolbutamide 1 g
	+ 1 min	80	14	
	+ 5 min	80	15	
	+ 10 min	70	14	
	+ 20 min	65	12	
	+ 30 min	65	9	
	+ 60 min	60	7	
	+106 min	55	5	
	+180 min	65	8	
	+270 min	65	5	
30/6	9.00 a.m.	75	5	Fasting

*Estimated by a modification of the method of Soeldner and Slone (1965).

blood glucose was still 75 mg/100 ml. The serum insulin response to tolbutamide was poor, and fasting insulin values were normal.

The patient's belongings had been searched on admission for insulin or other drugs, mainly because of her occupation, family history, and odd demeanour. Nothing was found. On further search after the normal tolbutamide test a bottle containing three 250-mg chlorpropamide tablets was found in her dressing gown. As final