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COMPARISON OF THE CARCINOEMBRYONIC ANTIGEN (CEA) IMMUNOASSAY AND
THE RADIOLOGIC COLON EXAMINATION IN THE DIAGNOSIS OF CARCINOMA
OF THE COLON: PRELIMINARY RESULTS

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In 1965, Gold and Freedman (1) were successful in isolating and identifying tumor specific antigens from specimens of adenocarcinoma in human colons. These authors subsequently were able to identify similar, if not identical, antigenic substances in other entodermally-derived tumors of the gastrointestinal tract and pancreas as well as in fetal gut, liver and pancreatic tissues between the second and sixth month of gestation. They, therefore, designated the substances as "carcinoembryonic antigens" (2). In 1969, Thomson, Krupey, Freedman and Gold reported on the development of an immunoassay for detection of circulating carcinoembryonic antigen (CEA) (3). They were able to demonstrate elevated CEA titers in 35 of 36 patients with known carcinoma of the colon. The CEA titer was not elevated in any patient with nonmalignant disease and was elevated in only three of 32 patients with carcinoma of other digestive organs (two stomach and one pancreas). The immunoassay method used by Thomson's group required careful precipitation and dialysis of samples prior to assay and subsequent co-precipitation of the antibody-CEA complex in saturated ammonium sulfate solution (method of Farr) (4). A simplified assay method involving co-precipitation of the antibody-CEA complex on zirconyl-phosphate gel has been developed by Hanson and associates (5). Lo Gerfo, Krupey and Hanson (6) have reported that this method has a sensitivity for detection of CEA in colonic cancer similar to that of the modified Farr technique (87% detection rate in 101 cases). Antigen however, has been identified in other nongastric carcinomas, as well as occasionally in benign diseases.

To date, all reported studies involve identification of the carcinoembryonic antigen in patients with previously established diagnoses. This communication presents the first prospective evaluation designed to compare the relative value of the CEA antigen assay and radiologic examination of the colon in the diagnosis and follow-up of patients with suspected colonic lesions.

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Such information is critical in determining the ultimate efficacy of any new technique purported to be useful in patients suspected of having new or recurrent colonic malignancy.

MATERIALS AND METHODS

During the three-month period beginning August 30, 1971 and ending November 30, 1971, a group of 316 patients had a blood specimen drawn for CEA assay in conjunction with a radiologic examination of the colon. The only pre-selection factor was that all patients had been referred for the radiologic examination. Written, informed consent was obtained from those patients willing to participate in the study. Less than 5% of the group refused to participate.

The serum level of carcinoembryonic antigen was determined by radioimmunoassay. The blood samples were collected in tubes containing ethylene diamine tetra-acetate salt (EDTA [Na₂]) and were processed within one hour of collection. The blood was centrifuged and the resultant plasma samples were frozen at -4° C until assay by the zirconyl-phosphate gel method of Hansen (6) could be performed.

Radiologic examination of the colon was performed by residents in Diagnostic Radiology at the University of Chicago Hospitals. Preparation consisted of two ounces of castor oil per os given the evening prior to the examination, except in patients with inflammatory bowel disease, and other cases in which rigorous preparation was contraindicated. Barium was introduced under fluoroscopic control, and multiple spot films of the colon were obtained--the standard examination included spot films of the lateral rectum, sigmoid colon, the splenic and hepatic flexures, and the cecum. Additional spot films were taken if deemed necessary by the fluoroscopist. An overhead 14 X 17 prone view of the filled colon was obtained, as well as a subsequent post-evacuation prone view. Each colon examination was reviewed by a staff radiologist, and

repeat examinations were ordered if any findings were equivocal. Air contrast examinations were performed if there was clinical suspicion of polyps or if the routine colon examination suggested the presence of a polyp.

RESULTS OF THE CEA TITER DETERMINATION

In 283 out of the 316 patients, adequate follow-up was available to allow preliminary evaluation. A value of 3 nanograms CEA/ml of serum was selected as the discriminating level between normal and elevated CEA titer. This level, though slightly higher than that previously reported in the literature (1,2,3,6,7) was selected because it gave the best discrimination between false positive and true positive values. Results are presented in Table 1. True positive titers were obtained only in 7 of 12 patients with new colonic malignancies and 3 of 4 patients with biopsy-proven recurrence of colonic carcinoma. Thus, the CEA-titer was accurate in 10 of 16 cases of proven colonic carcinoma. False positive titers were obtained in 39 of 226 patients whose ultimate work up and clinical course showed no evidence of carcinoma. Twenty additional positive titers were detected in patients with (a) malignancies of other organs (15 cases); (b) possible but nonconfirmed recurrence of colonic carcinoma (4 cases); and (c) colonic polyp of unknown histology (1 case).

RESULTS OF THE RADIOLOGIC EXAMINATION OF THE COLON

The results are summarized in Table 2. True positive results were obtained in 9 of the 12 patients with previously unsuspected carcinoma of the colon and 1 of 4 patients with biopsy-proven recurrence of colonic carcinoma. "False positive" results were obtained in five patients with benign colonic lesions (all five of these lesions were correctly identified as polyps). False negative diagnoses were obtained in 3 of 12 previously unsuspected colonic malignancies and 3 of 4 proven recurrences.

COMPARISON OF THE CEA ASSAY AND RADIOLOGIC EXAMINATION OF THE
COLON IN BENIGN CONDITIONS AND NONCOLONIC MALIGNANCY

104 of 131 patients without malignancy or bowel lesions had a normal colon examination and a CEA titer of below 3 nanograms of CEA/ml. The mean value for the CEA titer in this group was 1.3 nanograms of CEA/ml. An additional 27 patients had a normal colon examination, but a CEA titer greater than 3 nanograms of CEA/ml. Ten of these patients had either cirrhosis or renal disease. Both of these conditions have previously been associated with elevated CEA titer (7). In two patients, the elevated titer was probably due to medication [Heparin (1); ^{125}I (1)]. The elevated CEA titer was unexplained in 15 additional patients, although the follow-up period is too brief to exclude undetected malignancies.

In 47 patients, the radiologic colonic examination demonstrated one or more diverticula and no other lesion. Forty-one of these patients had normal CEA titers (less than 3 nanograms/ml) while there was a "false positive" elevation in six cases. Six of 29 patients with inflammatory bowel disease had a "false positive" titer elevation.

Elevated CEA titers were detected in 15 of 36 patients with noncolonic malignancies. The origin of the neoplasm in these patients included pancreas (2), liver, hepatoma (1), tongue, squamous cell (1), ovary (1), uterus (3), breast (2), kidney (1), bladder (1), lung (1), and unknown primary adenocarcinoma (2).

COMPARISON OF THE CEA ASSAY AND RADIOLOGIC EXAMINATION OF THE
COLON IN NEWLY DIAGNOSED COLONIC CARCINOMA

In 12 of the patients studied by the CEA assay and radiologic colon examination, a previously undetected adenocarcinoma of the colon was ultimately

found. The results of the CEA assays and radiologic examinations are summarized in Table 3. The radiologic examination was positive in 8 of these cases, suspicious in one case and did not detect the tumor in three cases. In only seven of the twelve cases, was the CEA titer significantly elevated. In five of these seven cases, the lesion was demonstrated on the radiologic examination, in one case, there was a suspicion of a lesion in the area in which the malignancy was ultimately discovered, and in one case the lesion was "missed" on initial examination, although in retrospect it should have been detected.

COMPARISON OF THE CEA ASSAY AND RADIOLOGIC EXAMINATION OF THE COLON IN RECURRENT COLONIC MALIGNANCIES

Seventeen patients studied had previous colonic resection for primary adenocarcinoma. The post-surgical period varied from five months to 14 years. Ten of these patients had normal CEA titers and no evidence of recurrence by radiologic examination; one of these patients, however, was subsequently proven to have tumor recurrence. Seven patients had elevated CEA titers. In three of these seven cases, biopsy-proof of recurrent tumor was obtained, although the recurrence was demonstrated by radiologic examination in only one of these patients. The remaining four patients with elevated carcinoembryonic antigen tumors have no evidence of recurrence either on the radiologic examination or by other methods utilized to date. All four patients, however, are in the five- to seven-month post-operative period, and this interval is considered too short to exclude recurrence.

DISCUSSION

Five newly diagnosed carcinomas of the colon had normal CEA titers. In three of these cases, the lesions were demonstrated on the radiologic examination of the colon as sessile polypoid masses (Fig. 1). In the two remaining cases, malignancy was discovered in polyps excised at proctoscopy. Both the CEA titers.

and the radiologic examinations were normal in these two cases. In one case, the colonic examination demonstrated a mass near the anal canal which was felt to represent an internal hemorrhoid, although the possible presence of a tumor was suggested in the initial radiologic report (Fig. 2). In this particular case, the CEA titer was elevated and would have probably encouraged further workup of the patient. In one newly diagnosed case of carcinoma of the colon, the CEA titer was elevated but the radiologic examination was interpreted as showing no evidence of malignancy. Extensive diverticulosis was present in this instance and a narrowed area was noted in the descending colon; the narrowing, however, was interpreted as being secondary to the diverticular disease. Three months later the patient developed symptoms suggestive of a partial bowel obstruction and a repeat colon examination was interpreted as probable carcinoma. The patient was proven at surgery to have carcinoma in the narrowed segment of the descending colon. In retrospect, we consider that this lesion should have been diagnosed as carcinoma on the initial colon examination (Fig. 3). It is, of course, possible that some of the remaining "false positive" CEA titer elevations may represent early detection of colonic carcinoma (or other noncolonic malignancies).

The group of 17 post-operative patients studied for recurrence of colonic tumor is of special interest. One of the patients with normal CEA titer subsequently was proven to have recurrence. In this case the normal titer was observed at the time of the six-month post-operative colon examination, which demonstrated an obstructive lesion at the anastomosis. Surgical exploration revealed only a perirectal abscess, which was drained, with an inflammatory stricture; surgical specimens showed no tumor recurrence at this time. Ten months post-operatively, however, there was a palpable mass at the anastomotic site. A repeat radiologic examination revealed marked irregularity at the

anastomosis, but in view of the previous history of abscess, a diagnosis of recurrent malignancy was not made (Fig. 4). Subsequent biopsy revealed recurrent tumor. In three of the post-operative patients, the CEA titer was elevated and biopsy proof of recurrent tumor was obtained. In two of the cases, the radiologic colon examination did not demonstrate evidence of recurrence. In one case, lung metastases were present. The remaining case was particularly interesting since not only the colon examination, but also proctoscopy with biopsy were initially negative for tumor recurrence, and only on a repeat proctoscopic biopsy was a diagnosis of recurrent adenocarcinoma established.

CONCLUSION

Our data indicate that the CEA test in its present form is unlikely to be a good single screening test for patients suspected of having carcinoma of the colon. The incidence of false positive titers (about 25%) is disappointing. Even if the specificity could be improved, the CEA assay only proved accurate in 7 of 12 new cases of colonic carcinoma in this series, while the radiologic colon examination detected 9 of these 12 cases. As a result, we conclude that at its current level of development the CEA-titer determination should be used in conjunction with the radiologic examination of the colon. The overall accuracy of the two techniques combined, 10 of 12 cases, is better than either test alone. At this time, the CEA assay appears to be more reliable in establishing the presence of recurrent carcinoma of the colon than the radiologic colon examination, though our series is still too small to be definitive.

Finally, since this is the first prospective series using the CEA assay ever reported, it is not surprising that the detection rate of the CEA assay on this study, approximately 65%, is less than the 90% figure previously described in the literature.

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FIGURE CAPTIONS

Fig. 1A-S.B.--A 3 cm sessile polypoid mass was demonstrated in the proximal rectum, which was considered to represent a villous adenoma, possibly malignant (solid arrow). A pedunculated polyp was present in the distal sigmoid colon (open arrow). The CEA titer was 2.4 ng/ml. Pathologic study of the surgical specimens proved the stalked polyp to be benign (adenomatous), but the sessile mass proved to be adenocarcinoma of the rectum (Modified Dukes' C1) arising in a villous adenoma.

Fig. 1B-D.W.--A 4 cm sessile polypoid mass was demonstrated at the hepatic flexure of the colon. The CEA titer was 1.7 ng/ml. Right hemicolectomy was performed and the lesion proved to be adenocarcinoma of the colon (Modified Dukes' C2). Metastases to the liver were demonstrated at surgery.

Fig. 1C-L.B.--A 1.5 cm sessile polypoid mass was demonstrated in the cecum. The CEA titer was 1.1 ng/ml. Right hemicolectomy was performed and pathologic study proved the lesion to be adenocarcinoma of the colon (Modified Dukes' C1).

Fig. 2--S.J.--An irregular mass was present in the distal rectum, adjacent to the anal canal. It was considered suspicious for carcinoma, but an internal hemorrhoidal mass was felt to be more likely. The CEA titer was 5.7 ng/ml. The lesion proved to be adenocarcinoma of the rectum by biopsy (Modified Dukes' B1).

Fig. 3--H.B.--Extensive diverticulosis was demonstrated throughout the colon with a narrowed area in the descending colon, which was initially thought to represent changes secondary to diverticular disease. The CEA titer was 5.5 ng/ml. The patient became clinically obstructed and surgery was required; pathologic study of the resected specimens revealed adenocarcinoma involving the narrowed area in the descending colon (Modified Dukes' B2). In retrospect, a diagnosis of carcinoma should have been made on the initial colon examination.

Fig. 4--J.F.--Marked irregularity of the colonic mucosa was demonstrated at the site of anastomosis ten months following resection for adenocarcinoma of the sigmoid colon. The patient had an abscess in this area, which was drained six months post-operatively. The changes demonstrated in this examination were interpreted as due to inflammation rather than recurrent malignancy. The CEA titer was 0.6 ng/ml. Biopsy revealed recurrent adenocarcinoma.

Table 1

	CEA Titer	
	Normal (Less than 3 ng/ml)	Abnormal (Greater than 3 ng/ml)
"Normal"	97	15
Cirrhosis	6	5
Chronic renal disease	0	3
Cirrhosis and chronic renal disease	1	2
Medications interfering with assay	0	2
Noncolonic malignancy	21	15
Diverticulosis	41	6
Inflammatory bowel disease	23	6
Carcinoma of colon (new cases)	5	7
Post-resection for carcinoma of colon (recurrent colonic carcinoma)	1	3
Post-resection for carcinoma of colon (no evidence of recurrence for more than 2 years)	9	0
Post-resection for carcinoma of colon (no evidence of recurrence in less than 1 year)	0	4
Polyps		
Proven benign by biopsy	8	0
No biopsy evidence	2	1
TOTAL	214	69

Table 2

	Radiologic Interpretation	
	Nonmalignant	Possible or Definite Malignancy
Normal, non-neoplastic or noncolonic malignancy (polyps excluded)	262	0
* Carcinoma of colon (new cases)	3	9
* Carcinoma of colon (recurrence)	3	1
Polypoid lesions	0	5
	<u>268</u>	<u>15</u>

* All cases pathologically proven.

Table 3
Newly Diagnosed Colonic Carcinoma (12 cases)

Patient Initials	CEA Titer (ng/ml)	Roentgenologic Interpretation	Modified Dukes' Classification	Distant Metastases
S.B.	2.4	3 cm sessile polypoid mass in proximal rectum and pedunculated polyp in distal sigmoid colon (Fig. 1A)	C1	--
D.W.	1.7	4 cm sessile polypoid mass at hepatic flexure of colon (Fig. 1B)	C2	Liver
L.B.	1.1	1.5 cm sessile polypoid mass in cecum (Fig. 1C)	C1	--
I.L.	1.7	Chronic ulcerative colitis without evidence of malignancy	C1	--
C.M.	1.3	Normal colon	B1	--
S.J.	5.7	3 cm irregular mass adjacent to anal canal (distal rectum) interpreted as probable internal hemorrhoidal mass although suspicious for carcinoma (Fig. 2)	B1	--
H.B.	5.5	Extensive diverticulosis of colon with narrowed segment in descending colon interpreted as secondary to diverticular disease [should have been interpreted as carcinoma in retrospect] (Fig. 3)	B2	--
H.U.	18.7	Large, constricting tumor mass in sigmoid colon with enterocolic fistulation	B2	Direct extension of tumor to small bowel
E.B.	> 20	6 cm obstructing mass at the hepatic flexure	B2	Liver
E.W.	> 20	Large, constricting tumor mass in the cecum	C2	--
A.M.	4.1	5 cm fungating polypoid mass in rectum	C2	--
B.P.	> 20	Large, irregular ulcerated mass in rectum	B2	--