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Correspondence

Ascitic Fluid "Humoral Tests of Malignancy"

To the Editor:

The recent paper by Jungst et al. (1) is another in a series of papers that propose a new ascitic fluid "humoral test of malignancy" (2, 3). The basic premise of these publications is that the ascitic fluid cytology is insensitive in detecting cancer as the cause of ascites formation. In general, cytologic analysis is said to detect *only* about two-thirds of patients with malignant ascites, as if *all* patients with malignant ascites should have peritoneal carcinomatosis (2, 3). However, in my experience, cytology has greater than 90% sensitivity in detecting peritoneal carcinomatosis, but is negative in patients with massive liver metastases and resulting portal hypertension-related ascites (Runyon, B. A. and Hoefs, J. C., *Hepatology* 1985; 5:1000, Abstract). The problem is that a significant fraction of patients that are included in the series of patients with intraabdominal tumor have *only* massive liver metastases without peritoneal carcinomatosis. Patients who have only massive liver metastases do not have positive ascitic fluid cytologies. It is my impression that investigators have assumed that the vast majority of cancer patients who develop ascites have peritoneal carcinomatosis as the cause of ascites formation. In fact, ascites caused by massive liver metastases is not rare. With careful investigation, massive liver metastases have been found to cause ascites in 26 to 33% of patients who have cancer and ascites; in general, patients have either peritoneal carcinomatosis or massive liver metastases, but not both (4; Runyon, B. A. and Hoefs, J. C., *Hepatology* 1985; 5:1000, Abstract). It is the inclusion of patients with massive liver metastases in series of malignant ascites that leads to the 67% sensitivity value of cytology. Cytology is much more sensitive when it is applied to the appropriate subgroup of malignant ascites patients—the patients with peritoneal carcinomatosis.

Ascitic fluid caused by peritoneal carcinomatosis is markedly different than fluid caused by massive liver metastases. The former has a high protein concentration and low serum-ascites albumin concentration gradient (unless the patient also has cirrhosis), and the latter has a low protein concentration and a high gradient (5). The ascitic fluid of patients with massive liver metastases is so similar to that of cirrhotic ascites that it is possible that some patients with massive liver metastases might have been erroneously classified into the cirrhotic ascites category of some studies. Fibronectin concentration (mean ± S.D.) in ascitic fluid caused by massive liver metastases-related ascites is 55 ± 21 μg per ml compared to 123 ± 45 μg per ml for peritoneal carcinomatosis; only 20% of massive liver metastases-related ascites specimens have a fibronectin concentration greater than 75 μg per ml (6), which is the proposed lower limit cut-off for malignancy (3). To analyze malignant ascites without subgrouping patients is to ignore the heterogeneity that is present in the series.

Another problem with 2 of the 3 papers on "humoral tests for malignancy" (1, 2) is that they did not include a control group of noncirrhotic, nonmalignant ascites samples. In my study, the fibronectin concentration of "miscellaneous" samples (pancreatitis, heart failure, renal failure, etc.) overlapped essentially completely with that of the malignant ascites samples (including both subgroups), rendering the test useless in discriminating between miscellaneous and malignant samples (6). In my study of ascitic fluid cholesterol and triglycerides (analyzed by Technicon Autoanalyzer), the overlap between groups was also excessive (see Figures 1 and 2). Although the cholesterol concentration of cirrhotic ascites samples (18 ± 13 mg per dl) was significantly ($p < 0.001$) lower than that of peritoneal carcinomatosis samples (83 ± 37 mg per dl) and significantly ($p < 0.02$) lower than massive liver metastases samples (43 ± 23 mg per dl), there was no difference between the cholesterol of miscellaneous samples (63 ± 30 mg per dl) and that of either subgroup (or the aggregate) of malignant samples. There were no differences between any groups regarding ascitic fluid triglyceride concentration in my study. Tests that cannot discriminate between malignant samples and miscellaneous samples are of limited value, in my opinion. It is unrealistic to expect any one ascites test to detect all patients with malignant ascites just as it was unrealistic to expect the plasma fibronectin test to detect all patients with cancer (7). What we need are better definitions of subgroups of malignant ascites patients and stratification of data into subgroups. What we do not need are more ascitic fluid "humoral tests of malignancy."

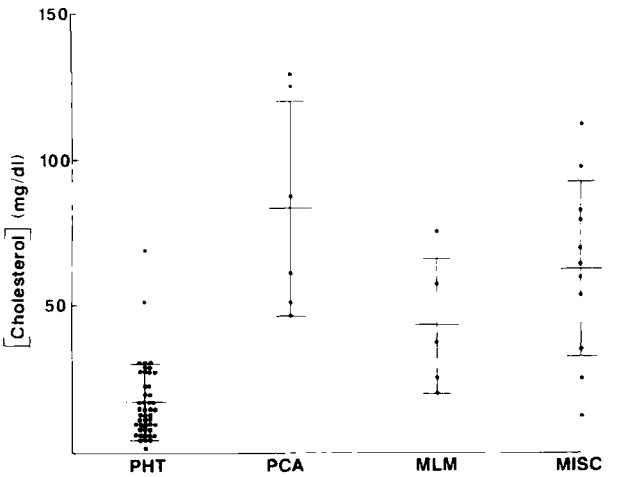

FIG. 1. Ascitic fluid cholesterol concentration in patients with sterile portal hypertension-related ascites (PHT) due to parenchymal liver disease, ascites due to peritoneal carcinomatosis (PCA), massive liver metastases (MLM) or miscellaneous causes (MISC).

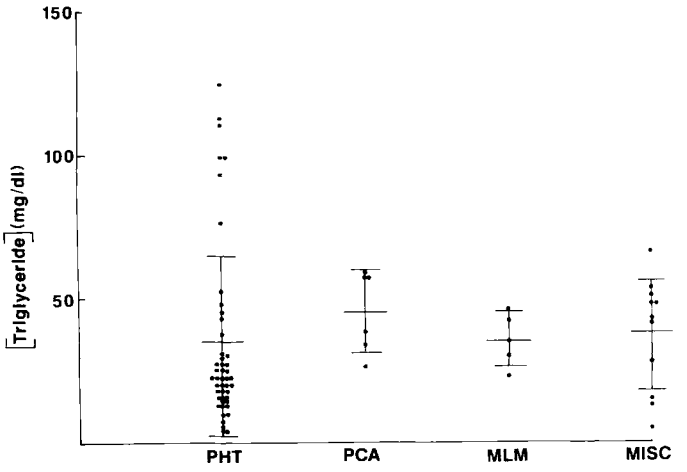

FIG. 2. Ascitic fluid triglyceride concentration in patients with portal hypertension-related ascites (PHT) due to parenchymal liver disease, ascites due to peritoneal carcinomatosis (PCA), massive liver metastases (MLM) or miscellaneous causes (MISC).

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Reply:

Runyon questioned the clinical usefulness of ascitic fluid cholesterol in the diagnosis of malignant ascites. He recommended a better definition of subgroups of malignant ascites patients and stratification of data into these subgroups. In the case of ascitic cytology, he reported a 90% sensitivity in detecting peritoneal carcinomatosis but usually negative results in patients with massive liver metastases. We agree that the inclusion of patients with massive liver metastases in series of malignant ascites may have been one reason that the sensitivity of ascitic fluid cytology was considerable lower in previous studies. In our study, it was our goal to discriminate ascites due to malignancies from ascites from nonmalignant causes by cholesterol analysis. Regarding this major aim, the argument of Runyon seemed to be of limited relevance.

As shown in Figure 1, all 23 patients with cirrhosis and portal hypertension had ascitic cholesterol concentrations below the discrimination value of 48 mg per dl. These findings were supported by Runyon's data. In comparison, only 4 from a total of 40 patients with malignant ascites (peritoneal carcinomatosis and massive liver metastases) revealed an ascitic fluid cholesterol below 48 mg per dl, 2 from 25 patients with positive ascitic cytology and 2 from 15 patients with negative cytology (Figure 1).

There is an overlap with cholesterol concentrations in ascites caused by heart failure and pancreatitis (miscellaneous causes), but the prevalence of these miscellaneous causes of ascites is low in our hospital. We agree with Runyon that elevated ascitic cholesterol is not a specific sign of malignancy, but in our experience and with the rather high prevalence of malignant ascites in our hospital, the probability of an underlying malignant disease in patients with elevated ascitic cholesterol exceeds 90%. Of course, the simple cholesterol measurement cannot offer a definitive diagnosis but may be a useful hint for the further diagnostic procedures in such patients.

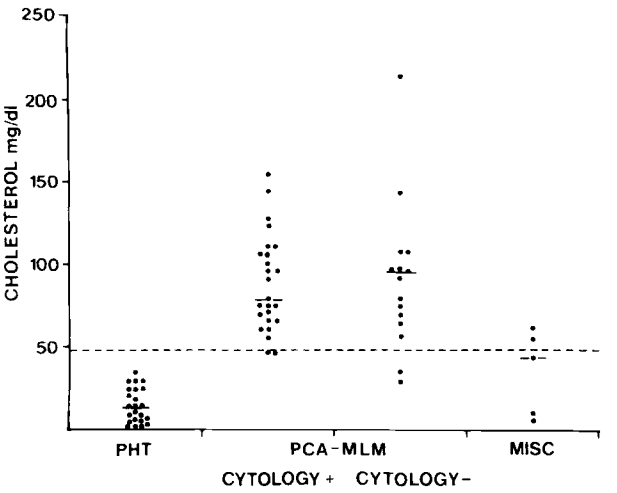

FIG. 1. Ascitic fluid cholesterol concentration in patients with sterile portal hypertension-related ascites (PHT) due to parenchymal liver disease, ascites due to peritoneal carcinomatosis (PCA), massive liver metastases (MLM) or miscellaneous causes (MISC).

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