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Present Status of Cancer Tests

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Since the onset of cancer occurs without perceptible symptoms and since it can be cured in its early stages, there have been many who have sought methods for early detection of this disease, particularly a method of screening that could be used quickly and inexpensively as a case-finding method. These methods may be roughly divided into three groups: (i) the measurement of some product of the cancer; (ii) the measurement of some change in the body resulting from the cancer; and (iii) the measurement of some change in the body that favors the development of a cancer.

In examining, in the literature, the claims for cancer tests, one should always keep in mind the type of patients used in the evaluation. After a cancer is well developed, many changes occur in the host that are not necessarily concerned with cancer but are the result of chronic disease. For example, it was shown by one of us (*1*) several years ago that the sedimentation rate test was positive in 69 percent of all well-developed cancers, whereas it was positive in only 48 percent of early, localized cancers. In an evaluation of a cancer test it is expedient to know whether the test is to be used as a method for finding cases of cancers or whether it is just an adjunct to other diagnostic methods.

In this paper (*2*) we discuss cancer tests from the standpoint of a case-finding method only. It is quite possible that a test not useful as a screen would be useful as a diagnostic aid. Dunn and Greenhouse (*3*) have set up excellent criteria that are important to follow in the evaluation of a cancer test. These authors showed that a test in order to be of value must be positive in 90 percent of *early, localized* cancer and that there should be only 5 percent false positives.

Many workers in recent years in their evaluation of a cancer test have overlooked Dunn and Greenhouse's statement that the cancer test should be 90-percent positive in early, localized disease. Cancer tests too frequently have been evaluated on hospital patients whose disease, although still localized, was fairly extensive. A test may be positive in a high percentage of these, not for reasons primarily associated with cancer, but for reasons that may be absent in early cases. Dunn and Greenhouse (*3*) considered the 5 percent false positives permissible. It does not make too much difference whether a cancer test is positive in other well-defined diseases such as tuberculosis or cirrhosis. It is unlikely that these diseases will be found, at least in any numbers, in a case-finding survey of the general population. However, for the test that is to be used as a cancer case-finding method on the general population, it does make considerable difference whether the test is positive for minor conditions that are likely to be found in fairly high numbers in the general population.

We have found that a good method for the evaluation of a cancer test is to take for study all the patients who come to a cancer clinic with skin and breast lesions and with suspicious cervical changes. In this way we obtain a large number of patients with early and localized cancer. Blood is taken on all these patients, and the tests to be evaluated are run in duplicate. We have recently tried this method on three tests. The first is the Penn test, which was first described by Penn and his group in 1952 (*4*) and which they have modified on several occasions. Some of us have had the privilege of working with Penn and his associates with this test. The reaction is a very interesting one and gives a high percentage of positive tests in the serums of patients with moderately advanced cancer; the one exception is that in cancer of the breast the reaction is frequently negative. The flocculant used in this test is derived from a choladienic ester and was kindly supplied to us by the Lederle Laboratories of the American Cyanamid Co.

The second test used is a modification of the Penn flocculant and was developed by two of us. The chemical nature of this flocculant has been described by us (*5*), and since one difference between this and Penn's flocculant is a chlorine radical, we have called it a chloral flocculant. This flocculant is somewhat more soluble than Penn's, and this may contribute to the higher number of positives we obtained.

The third test is the C-reactive protein antiserums test that was first described in 1930 (*6*). The antiserums were made available to us by Schieffelin and Co. It is a test that is highly specific for inflammation. The results of our evaluation of this test and the two other tests are shown in Table 1. It may be seen from this table that, although the number of cancers that gave positive reactions is quite high, the positives do not reach 90 percent. It may also be noted that, although the percentage of positives obtained with the chloral test is generally higher than that obtained with the Penn test, this advantage is nullified by the fact that the number of positives from patients with noncancerous conditions was also increased. It should be remembered that all the patients in this series were patients with cancer in its earliest stages, and that the cancer diagnosis of all patients listed as having cancer was verified by biopsy.

We were quite interested that the C-reactive protein antiserums test gave results similar to, but not identical with, those obtained with the flocculation tests. Since inflammation is almost always associated with cancer, we took six serums that gave highly positive precipitates with both the Penn flocculant and the

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Table 1. Evaluation of cancer tests

	Penn			Chloral			C-reactive		
	No.	Test positive		No.	Test positive		No.	Test positive	
		(No.)	(%)		(No.)	(%)		(No.)	(%)
Squamous cancer of skin	19	9	47.3	19	13	68.4	18	12	66.6
Basal cancer of skin	13	8	61.5	13	11	84.6	13	11	84.6
Cancer of cervix (invasive)	3	3	100	3	2	66.6	3	3	100
Intraepithelial cancer of cervix	16	7	43.7	16	9	56.2	13	7	53.8
Cancer of breast	6	2	33.3	6	5	83.3	3	3	100
Cancer of other organs	9	5	55.5	9	7	77.7	9	9	100
Noncancerous skin lesions	19	10	52.6	19	12	63.1	18	10	55.5
Noncancerous cervical lesions	26	8	30.7	26	16	61.5	23	13	56.5
Noncancerous breast lesions	6	2	33.3	6	2	33.3	5	3	60
Other noncancers	5	3	60	5	2	40	4	2	50

chloral flocculant and absorbed all the C-reactive protein from the serums with C-reactive protein antiserums. These serums were then negative with both the Penn and chloral flocculants. On this basis we believe that these two tests give positive reactions because of inflammation in the cancer and therefore are negative in the early stages of cancer when inflammation is minimal.

The three flocculation tests described are obviously based on the measurement of changes produced by cancer and other chronic diseases. For some time investigators have been intrigued by the possibility of measuring the changes that are predisposed to the development of cancer. It appears from the work of Dobriner and others (*7*) that hormonal imbalance would be an excellent body change to measure. With this in mind, we have attempted to conjugate a steroid with a protein in order to make an antigenic compound. Although such a conjugation of protein and steroid is possible, the linkages that we have tried so far are quickly broken after they are injected into an animal, and consequently only antibodies to protein are formed.

Although these approaches to the cancer-detection problem have so far been unavailing, the approach that consists of studying products of cancer has been successful. Fishman and Homburger (*8*) have reported considerable success with phosphatase studies on patients with cancer of the prostate. We have had marked success with the use of exfoliative cytology as described by Papanicolaou (*9*) for the early detection of cancer of the cervix. In this laboratory during the past few years we have been making a survey of the women in Memphis and Shelby County by the vaginal smear technique (*10*). It is our plan to study these women three times at yearly intervals.

From the female population of 200,000, we have so far examined 90,000 women once and another 25,000 a second time. The details of this study will be reported elsewhere (*11*). The results, however, show that we have an excellent procedure for finding cases of cancer. Of each 1000 women examined, whether they came from the charity clinics or were women of a higher economic status, we found that 982 could be told that they were all right for another year. Of the 18 in each 1000 whom we were not able to assure that they did not have cancer, 15 consented to have biopsies performed. These biopsies showed four invasive cancers and four intraepithelial cancers; of the remaining seven, two had lesions that were not cancerous but should be followed up, we thought. The remaining five were essentially negative.

We do not wish to classify these 18 in each 1000 as positive reactions; we prefer to consider this technique a cancer screen. As a screen it is very effective, because it eliminates 982 women of each 1000 from the necessity for further study. We are not yet able to say how many of the 982 had cancer that was missed, but preliminary studies of the first 25,000 women that were studied a second time showed that less than two in 1000 had early cancer that had been missed or had developed since the first test. The number of false negatives is so small, the likelihood of their being missed in the second examination is so slight, and the cancer in these is so early that these persons can receive effective treatment when the cancer is detected the second year.

There are two reasons for the success of this program. The first, and by far the most important, is the fact that the test is not thought to be a diagnostic test for cancer but merely a screen for the selection of suspicious cases for further study by biopsy. Since we are not concerned with the biopsy of a false positive test, we are not inhibited from biopsying all suspicious cases. However, even when this is done, 98 percent of the women examined are given a clean bill of health with regard to cancer for at least a year. The second reason is the *esprit de corps* that stems from the size of the program and the technicians' working together. Maintaining this has reduced the human error, which is at a minimum. In fact, there have been several instances in which technicians in the group have done excellent work, but when they moved to an isolated laboratory, the quality of their work suffered.

We have reviewed the status of several cancer tests and have pointed out that false hopes for a test are frequently the result of failure to evaluate the test with early cases. The result is that some condition, such as inflammation associated with moderately advanced cancer, is studied rather than something fundamental to cancer. Consequently early cancers are missed. It is pointed out that the use of the Papanicolaou smear technique in the early phases of cancer is an excellent screening test.

References and Notes

1. J. W. Kyle, S. G. Richmond, D. H. Sprunt, *Public Health Repts.* 68 (1953), U.S. Public Health Service Publ. No. 275. [*Evaluation of Cancer Diagnostic Tests,* Public Health Monogr. No. 12 (Government Printing Office, Washington, D.C.), p. 29.]
2. This study was supported in part by research grants CS-9053 and C-2249 from the National Cancer Institute, U.S. Public Health Service.
3. J. E. Dunn and S. W. Greenhouse, *Public Health Service Publ.* No. 9. (Government Printing Office, Washington, D.C., 1950).
4. H. S. Penn, *J. Natl. Cancer Inst.* 12, 1389 (1952); A. H. Dowdy *et al., Proc. Am. Assoc. Cancer Research* 1, 12 (1954).
5. F. C. Chang and D. H. Sprunt, *J. Am. Chem. Soc.* 76, 3213 (1954).
6. W. S. Tillett and T. Francis, Jr., *J. Exptl. Med.* 52, 561 (1930).
7. K. Dobriner *et al., Science* 95, 534 (1942).
8. W. H. Fishman *et al., J. Clin Invest.* 32, 1034 (1953); W. H. Fishman and F. A. Lerner, *J. Biol. Chem.* 200, 89 (1953).
9. G. N. Papanicolaou and H. F. Traut, *Diagnosis of Uterine Cancer by the Vaginal Smear* (Commonwealth Fund, New York; Harvard Univ. Press, Cambridge, Mass., 1943).
10. J. E. Dunn and D. H. Sprunt, *Public Health Repts.* 70, 341 (1955).
11. C. C. Erickson and J. E. Dunn, *Acta-Unio Intern. Contra Cancrum,* in press.