THE WILL ROGERS PHENOMENON

Stage Migration and New Diagnostic Techniques as a Source of Misleading Statistics for Survival in Cancer

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Abstract We found that a cohort of patients with lung cancer first treated in 1977 had higher six-month survival rates for the total group and for subgroups in each of the three main TNM stages (tumor, nodes, and metastases) than a cohort treated between 1953 and 1964 at the same institutions. The more recent cohort, however, had undergone many new diagnostic imaging procedures. According to the "old" diagnostic data for both cohorts, the recent cohort had a prognostically favorable "zero-time shift." In addition, by demonstrating metastases that had formerly been silent and unidentified, the new technological data resulted in a stage migration. Many patients who previously would have been classified in a "good" stage were assigned to a "bad" stage. Because the prognosis of those who migrated, although worse than that for other members of the good-stage group, was better than that for other members of the bad-stage group, survival rates rose in each group without any change in individual outcomes. When classified according to symptom stages that would be unaltered by changes in diagnostic techniques, the two cohorts had similar survival rates. (N Engl J Med 1985; 312:1604-8.)

ALTHOUGH cancers are usually "staged" according to morphologic evidence of the tumor's anatomical dissemination and histologic type, the prognosis can also be affected by nonmorphologic features of the patients' clinical condition. Among these clinical features are the pattern of symptoms, the severity of illness, the tumor's rate of growth, and comorbidity with other diseases. These clinical features have been shown to result in major prognostic distinctions among patients who otherwise seem similar when classified only according to morphologic categories for cancers of the lung,[1-3] rectum,[1,2,4,5] larynx,[6] breast,[7,8] and endometrium[9] and for Hodgkin's disease[10] and acute leukemia.[11]

The prognostic impact of clinical distinctions in lung cancer was demonstrated in a cohort of patients[3] first treated during the period from 1953 to 1964, and the research reported here was undertaken to determine whether the same distinctions still pertained with more recent diagnostic and therapeutic methods. The main results of the research indicate that the distinctions still exist, but the study also revealed an interesting byproduct, which is the subject of this report.

BACKGROUND

Original Study Design

The original purpose of this study was to analyze the clinical presentation, paraclinical data (roentgenograms, bronchoscopic findings, microscopical evidence, laboratory tests, and so forth), therapy, and subsequent course of all patients who received a microscopically confirmed diagnosis of primary lung cancer and initial therapy for that disease at Yale–New Haven Hospital or the West Haven Veterans Administration Medical Center between January 1 and December 31, 1977. The year 1977 was chosen to allow a five-year follow-up period for survival when the research began in 1982.

Our original plan was to compare the results in the 1977 cohort of patients with the results in a cohort of similar patients who had undergone initial treatment at the same two hospitals during the period from 1953 to 1964. For information contained in the medical records of the recent cohort, we planned to employ the same data-processing mechanisms, which have been extensively described elsewhere,[12-15] that had been used to acquire and analyze data for the previous cohort. Although all the previous data-processing techniques were readily applicable, we quickly found that the formats did not provide for several new kinds of technological information contained in the records of the recent group. In particular, the 1953-1964 cohort had not undergone the new forms of diagnostic imaging (radionuclide scanning, computerized tomography, and ultrasonography) that have been developed and extensively used since 1964. Our old data-management formats were therefore expanded to include the new diagnostic information for the 1977 cohort.

In the first analyses of the results assembled for the 1977 cohort, all the available morphologic evidence — from physical, imaging, microscopical, or other examinations — was used to classify patients according to the standard categories of the TNM (tumor, nodes, and metastases) staging system for cancer.[16] The results showed that survival rates for the entire 1977 cohort and for subgroups at each of the three main TNM stages were higher than corresponding rates for the 1953-1964 cohort.

When we classified the 1977 group of patients according to clinical features of their symptoms and comorbidity, we found the same types of prognostic-gradient phenomena that had been noted in the previous cohort: within the same TNM morphologic stage, distinctions in the severity of clinical manifestations were associated with major prognostic differences in survival. Although these results confirmed our original hypothesis that improvements in diagnosis and therapy

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have not altered the prognostic importance of clinical manifestations, we began to wonder, on further reflection, about the improved survival rates noted in the 1977 cohort.

Statistical Problems

Epidemiologists have described a phenomenon called "zero-time shift," or "lead-time bias," which can extend the statistical length of a patient's survival without necessarily prolonging the duration of life.[17,18] This phenomenon occurs when a screening test or other appropriate diagnostic procedure leads to the detection of a disease before symptoms have developed. Even if therapy is ineffectual, the period of survival will be increased by the increment provided by presymptomatic detection of the disease.

The lead-time problem was pertinent in our research, but we were also concerned about another problem. The additional issue arose not from presymptomatic detection of a tumor but from "early" detection of the cancer's metastases, before they became evident either as symptoms or with physical or conventional roentgenographic examination. If the new methods of diagnostic imaging were routinely finding metastases that were "silent" or "early," the TNM stages for the more recent patients would not be assigned according to the same data as in the preimaging era. The new data would allow patients with silent metastases to "migrate" from lower TNM stages (such as I and II) into higher ones (such as II and III). The migration would improve survival in the lower stages, because fewer patients with metastases would be assigned to them. Migration would also improve survival in the higher stages, since the metastases in the newly added patients were silent rather than overt. Although the total survival rate in the cohort would be unaffected, the stage-migration phenomenon could improve the survival rates in each of the constituent stages.

As we contemplated this migration and its unusual statistical effects in improving the parts without altering the whole, Dr. Michael McFarlane called our attention to a remark made by the humorist-philosopher, Will Rogers, about a geographic migration during the American economic depression of the 1930s. Rogers said, "When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states." We have not been able to find the exact citation for this remark, and we have heard about similar comments that have been ascribed to other sources. Nevertheless, since Rogers' humor had many salubrious effects that were never honored medically and since we doubt that any conflict will arise about scientific priority for the eponym, we propose that the taxonomic and statistical consequences of stage migration be called the "Will Rogers phenomenon."

This report contains empirical evidence of the phenomenon, a discussion of the distortions it produces, and suggestions about how to manage the problems.

Methods

For the particular research reported here, each member of the two cohorts was classified according to the patient's status at "zero time," which was the date of the first antineoplastic treatment for lung cancer. In patients who had not undergone thoracotomy, radiotherapy, chemotherapy, or surgical excision of a metastatic lesion, zero time was the date of the decision not to provide treatment. Although the prerequisite microscopical evidence of cancer could have been obtained before or after zero time (e.g., at the time of thoracotomy), the zero-time classification of the anatomical or other stage depended exclusively on data that had been acquired before zero time.

In the 1953-1964 cohort, the zero-time classification of TNM stages depended on evidence obtained by physical examination, bronchoscopy or other endoscopy, biopsy and cytology, and conventional roentgenographic procedures (e.g., plain films, ordinary tomography, and films made with ingested or injected contrast medium). All this information, which was also available for the recent cohort, was designated as "old-stage data" when used to classify the members of either cohort. The additional information obtained with modern imaging procedures was available only for the recent cohort. Since the newer information had been obtained and coded separately, the recent cohort could be classified either with old-stage data alone or with "new-stage data," which included both the traditional and the newer information. Using the customary, standard criteria for TNM staging in lung cancer,[16] we classified each patient as being in Stage I, II, or III. The classification could have been made with either new-stage data or old-stage data for the 1977 cohort but depended solely on old-stage data for the 1953-1964 cohort.

The clinical manifestations of disease at zero time were also classified as asymptomatic, primary, systemic, or metastatic, according to a previously described taxonomy for the symptomatic presentation of patients with cancer of the lung.[3] The characteristics of this classification are outlined in Table 1. Because it depends on overt clinical manifestations rather than on technological evidence, the symptom stage could be assigned in a similar manner for both cohorts.

Although information on therapy and the subsequent clinical course was excerpted from the medical record and coded for each patient, the information is not pertinent to the analysis here. Each patient was classified according to zero-time status before therapy, and the classification was correlated with the patient's subsequent survival, irrespective of therapy. The outcome results are cited as rates (or proportions) of survivors at a point six months after zero

Table 1. Taxonomy for Classification of Symptoms of Lung Cancer.*

Metastatic: Symptomatic evidence of a metastatic lesion. This category excludes patients with morphologic evidence of a metastasis but no symptoms or other appropriate clinical manifestations. The category includes patients with quasi-metastatic disease in which clinical manifestations are strongly suggestive of metastasis but without morphologic confirmation.

Systemic: Symptoms of anorexia, weight loss, or fatigue, or existence of a paraneoplastic syndrome (such as hypertrophic periosteopathy). This category includes patients with appropriate symptoms that may be due to the cancer or to a comorbid ailment (or both).

Primary: Symptoms that are (or can be) attributed to the lung cancer at its primary locus. Among such symptoms are hemoptysis, a recent change in the pattern of a cough, recent development of a subjectively noted wheeze, a recent change in the pattern of dyspnea, an appropriate form of chest pain (e.g., not angina pectoris), or clinical manifestations (such as fever) of roentgenographic evidence of acute pulmonary inflammation. If coexisting pulmonary ailments, such as chronic obstructive lung disease, preclude determination of an exact source for the symptoms, the primary-symptom category is used whenever such symptoms appear, regardless of whether pulmonary comorbidity is present.

Asymptomatic: None of the foregoing symptoms. Patients in this category are usually identified during a screening examination or on the basis of a chest film obtained for other reasons.

*Patients were classified, in the manner of TNM (tumor, nodes, and metastases) staging systems, according to the most severe symptoms on presentation. Symptom stages are listed in order of decreasing severity.

time for each patient. The six-month point was chosen because it approximates the median survival of patients with lung cancer,[3] thus allowing the overall survival rate at six months to be about 50 per cent — a relatively high proportion for which statistical changes and distinctions can readily be shown. We used survival rates rather than median survival in each group because the numerators and denominators clearly indicate the number of patients in each stage, as well as identifying both the patients who migrated from one stage to another and the statistical consequences of the migration in certain results for the cohort.

To determine statistical significance, we used the chi-square procedure or Fisher's exact test (when appropriate); all results cited as significant had a P value under 0.05.

Results

As compared with the 1266 patients in the 1953-1964 cohort, the 131 patients in the 1977 cohort were more likely to have been treated at Yale–New Haven Hospital than at West Haven Veterans Administration Hospital (76 vs. 68 per cent), and the 1977 cohort had more women (27 vs. 12 per cent), a similar median age (63 years), and a higher proportion of blacks (9 vs. 4 per cent). None of these differences was quantitatively important in the analysis of morphologic and clinical distinctions.

Table 2 shows the frequency and results of the new diagnostic imaging procedures in the 1977 cohort. Proportions of tested patients were particularly high (75, 60, and 56 per cent, respectively) for radionuclide scans of liver–spleen, brain, and bone. (The proportions of patients undergoing these tests are probably slightly higher today, in 1985, and the proportions undergoing other tests are substantially higher, since their popularity has increased in the past seven years.)

Table 2 also indicates a source of substantial ambiguity in the TNM classification. Since a patient's TNM classification differs according to whether equivocal results are regarded as positive or negative, an arbitrary decision must be made about what to call them. The various published descriptions of TNM staging provide no guidance for this decision. We chose to classify the equivocal results as positive, because various oncologic colleagues have stated that patients with equivocal results are usually regarded as having metastatic lesions when treatment is selected and evaluated. (The staging results show the same trend with either a positive or negative classification, but the distinctions are more striking when the equivocal results are regarded as positive.)

Table 2. Frequency and Results of New Diagnostic Imaging Techniques in the 1977 Cohort.*

Imaging Procedure	Tested Patients *	Results of Test	
		Positive	Equivocal
	no. of patients (%)		
Liver–spleen scan	98 (75)	10 (10)	6 (6)
Brain scan	79 (60)	8 (10)	4 (5)
Bone scan	73 (56)	12 (16)	17 (23)
CT scan of head	12 (9)	7 (58)	0 (0)
Abdominal ultrasound	14 (11)	2 (14)	5 (36)
Gallium scan †	32 (24)	10 (31)	10 (31)
Other ‡	9 (7)	5 (56)	1 (11)

*Patients were counted only once in each category, even if tests were repeated.

†Stage assignments were affected by positive or equivocal results at any locations beyond the primary site.

‡CT scan of a part of the body other than the head or ultrasound outside the abdomen.

Table 3. Six-Month Survival Rates and Composition of Cohorts, Using All Available Data for TNM Stages in the Two Cohorts.*

TNM Stage	Six-Month Survival		Proportion of Patients in Each Stage	
	1953-1964 cohort "old data"	1977 cohort "new data"	1953-1964 cohort	1977 cohort
	no. of patients (%)		*% of patients*	
I	211/281 (75)	22/24 (92)	22	18
II	98/172 (57)	13/18 (72)	14	14
III	242/813 (30)	37/89 (42)	64	68
Total	551/1266 (44)	72/131 (55)	100	100

*TNM denotes tumor, nodes, and metastases.[16]

Table 3 shows the six-month survival rates that we first examined in the two cohorts, with each cohort classified according to all the available data — i.e., old-stage data for the 1953-1964 cohort and new-stage data for the 1977 cohort. As compared with the previous group, the recent cohort had survival rates that were significantly higher both for the entire group and for patients at each TNM stage. Furthermore, the improved survival did not seem to be attributable to a lead-time bias, since the recent cohort had a somewhat smaller proportion of patients included in the "good" Stage I (18 vs. 22 per cent) and a somewhat larger proportion included in the "poor" Stage III (68 vs. 64 per cent). Results of this type in reports of post-treatment survival have served as a basis for the belief that modern therapy has substantially improved survival rates among patients with cancer.

The accomplishments suggested by this belief become somewhat more difficult to justify, however, when the TNM classification of the recent cohort is made only according to the data used in classifying the previous cohort. With the old staging data, as shown in the left-hand column of Table 4, the total six-month survival rate for the recent cohort was the same, but the proportions of patients assigned to the TNM stages changed, as did the six-month survival rates for patients at each stage: 32 of 42 (76 per cent) for Stage I, 17 of 25 (68 per cent) for Stage II, and 23 of 64 (36 per cent) for Stage III. These rates were still somewhat better than the corresponding rates at each stage for the previous cohort, but the differences were no longer statistically significant.

The most striking result of the old-data classification of TNM stages is a clear demonstration of a zero-time shift in the recent cohort. On the basis of the old data, the patients in the recent cohort were distributed as follows: Stage I, 32 per cent (42 of 131); Stage II, 19 per cent (25 of 131); and Stage III, 49 per cent (64 of 131). Thus, when staged with the same kinds of data used for the previous cohort, the recent cohort had a significantly higher proportion of Stage I patients (32

Table 4. Effects of Stage Migration on Six-Month Survival Rates in the 1977 Cohort.*

OLD-DATA TNM STAGE *	STAGE MIGRATION	NEW-DATA TNM STAGE *
	six-month survival	
I: 32/42 (76)	→ I: 22/24 (92)	I: 22/24 (92)
	↗ II: 1/1 (100)	
	↗ III: 9/17 (53)	
II: 17/25 (68)	→ II: 12/17 (71)	II: 13/18 (72)
	↗ III: 5/8 (63)	
III: 23/64 (36)	→ III: 23/64 (36)	III: 37/89 (42)
	Total 72/131 (55)	

*TNM denotes tumor, nodes, and metastases.[16] Values are numbers of patients, with percentages in parentheses.

vs. 22 per cent) and a significantly lower proportion of Stage III patients (49 vs. 64 per cent).

The migration that led to the statistical improvements in the survival of the 1977 cohort is shown in the remainder of Table 4. The patients who migrated from one stage to another on the basis of the new data are shown in the middle column. The combined results of the new-data classification are shown on the right.

As indicated in Table 4, the new data resulted in a migration of 18 patients out of the old Stage I, all but one of whom migrated to Stage III. These 17 Stage III newcomers had a six-month survival rate (53 per cent) that was lower than the original survival rate in Stage I (76 per cent) but higher than the original rate in Stage III (36 per cent). The eight patients who migrated from Stage II to Stage III also had a survival rate that was lower than the rate for the rest of the Stage II group but higher than the rate for the rest of the Stage III group. Consequently, the survival rate was higher for patients at each of the new-data TNM stages, whereas the overall 55 per cent survival rate for the cohort was unaffected.

Although the results of this morphologic analysis clearly show the zero-time shift and stage migrations caused by improved diagnostic imaging, the same phenomena can also be examined according to the classification of symptoms. Because this classification is not affected by morphologic information, the symptom stages are unaltered by differences in diagnostic imaging from one era to the next. The symptom classifications used from 1953 to 1964 would involve the same type of evidence and would be just as pertinent as those used in 1977. Symptom classifications can thus help clarify both issues under consideration. First, the proportion of patients in each cohort with the favorable symptom stages would help indicate the zero-time shift arising from an increased use of screening procedures (Table 5). Second, the survival rates in the two cohorts would be particularly suitable for comparison of patients stratified according to symptom stages that have not changed during the past 30 years (Table 6).

Table 5. Composition of the Two Cohorts According to Symptom Stage.

SYMPTOM STAGE	1953-1964 COHORT (N = 1266)	1977 COHORT (N = 131)
	no. of patients (%)	
Asymptomatic	84 (7)	18 (14)
Primary	298 (24)	61 (47)
Systemic	305 (24)	20 (15)
Metastatic	579 (46)	32 (24)

Table 5, which shows the proportions of patients assigned to each symptom stage, strongly demonstrates the zero-time shift in the composition of the two cohorts. The asymptomatic group accounted for 7 per cent of the previous cohort and 14 per cent of the recent cohort, and the primary-symptom group accounted for 24 per cent of the previous cohort and 47 per cent of the recent cohort. Thus, the proportion of patients assigned to the two most favorable symptom stages was twice as high in the recent cohort (60 per cent) as in the previous cohort (30 per cent). At the other end of the spectrum, the proportion of patients in the 1977 cohort who had metastatic symptoms was almost half that in the earlier cohort (24 vs. 46 per cent, respectively).

Table 6. Six-Month Survival Rates According to Symptom Stages.

SYMPTOM STAGE	SIX-MONTH SURVIVAL	
	1953-1964 COHORT	1977 COHORT
	no. of patients (%)	
Asymptomatic	65/84 (77)	14/18 (78)
Primary	186/298 (62)	41/61 (67)
Systemic	152/305 (50)	10/20 (50)
Metastatic	148/579 (26)	7/32 (22)
Total	551/1266 (44)	72/131 (55)

Table 6 shows the six-month survival rates when the patients of the two cohorts were stratified according to symptom stages. The data clearly demonstrate that the higher overall survival of the 1977 cohort was due to the effect of the zero-time shift in producing a better prognostic composition of the cohort. Within each of the four stages, the six-month survival rates for the two cohorts were similar. The previous cohort had slightly better results in the metastatic group, and the recent cohort fared slightly better in the asymptomatic and primary-symptom groups, but none of the differences was clinically or stochastically impressive.

DISCUSSION

These results are distressing because they suggest that the contemporary improvement of survival rates, at least among patients with lung cancer, is a statistical artifact. We would have guessed initially that improvements in ancillary support — with such therapeutic agents as steroids, antibiotics, and blood products — would have led to better survival rates in the

recent cohort even if no major benefits could be attributed to advances in surgery, radiotherapy, and chemotherapy. A possible explanation for the observed standoff is that the advances in both antineoplastic and supportive therapy have indeed been beneficial in some patients but have produced detrimental complications in others, so that the opposing effects in different patients have counterbalanced one another statistically. Because of the relatively small size of our 1977 cohort, we did not attempt any further exploration of this possibility, which awaits future research.

The artifact that produces the false sense of contemporary therapeutic accomplishment arises because of inadequate attention to two important problems: the quantitative effects of improved diagnostic techniques, and the taxonomic need to classify the symptomatic status of patients as well as the morphology of cancers. In a simple analogy, the quantitative problem occurs if we measure maturation time without recognizing different initial mixtures of ripe and unripe fruit; the taxonomic problem occurs because the label of "fruit" does not distinguish among different mixtures of apples, oranges, and grapes. These two problems produce the statistical confusion that is ordinarily disguised as lead-time bias and as stage migration.

The quantitative problem has been recognized, although not emphasized, in discussions of the prognosis for cancer of the lung[19] and for osteosarcoma.[20] The extent of the problem is unclear, because it has not yet been investigated for other cancers, and no documentary data are available for suitable comparisons of the differences in old and new morphologic staging.

It might be argued that our comparisons of old-stage and new-stage data in the 1977 cohort were biased by the impact of new diagnostic imaging. For example, to avoid making invidious retrospective decisions about the reasons why certain tests were ordered, we accepted the results of the recent test as old-stage data if that same test was readily available and could have been performed in the 1953-1964 period. Consequently, the results of a positive liver biopsy in the recent cohort were regarded as old-stage data, but the biopsy might not have been performed without the suggestion of metastases provided by a liver–spleen scan. The argument about a biased comparison is therefore quite plausible; but the bias, if present, would have acted to reduce rather than increase the magnitude of the observed migration in stages. If the liver biopsy had provided the only evidence of distant metastasis, the patient would have been assigned to Stage III on the basis of both the old and the new data. If the results of the scan-provoked liver biopsy had not been accepted as old data, however, the patient would have been assigned to Stage I (or II) with the old data, thus increasing the numbers of people for whom new data resulted in a migration to Stage III.

The taxonomic problem that quantitatively produces the Will Rogers phenomenon can be resolved with better attention to a hallmark of good scientific research: reproducible specification of the "material" under investigation. This specification cannot be achieved with a system of classification that characterizes the morphology of a tumor while ignoring the rest of the patient. The persistent neglect of a suitable clinical taxonomy for patients with cancer has had many deleterious effects, discussed elsewhere,[21,22] on both the humanistic and scientific quality of oncologic therapy. Although "Will Rogers" can be an eponym for an important scientific problem in medical statistics, the solution of the problem will require intensive scientific and clinimetric[23] attention to the types of distinctively human phenomena whose observation and analysis made Will Rogers famous.

References

1. Feinstein AR. Symptoms as an index of biological behaviour and prognosis in human cancer. Nature 1966; 209:241-5.
2. *Idem.* A new staging system for cancer and a reappraisal of "early" treatment and "cure" by radical surgery. N Engl J Med 1968; 279:747-53.
3. Feinstein AR, Wells CK. Lung cancer staging: a critical evaluation. Clin Chest Med 1982; 3:291-305.
4. Feinstein AR, Schimpff CR, Hull EW. A reappraisal of staging and therapy for patients with cancer of the rectum. I. Development of two new systems of staging. Arch Intern Med 1975; 135:1441-53.
5. *Idem.* A reappraisal of staging and therapy for patients with cancer of the rectum. II. Patterns of presentation and outcome of treatment. Arch Intern Med 1975; 135:1454-62.
6. Feinstein AR, Schimpff CR, Andrews JF Jr, Wells CK. Cancer of the larynx: a new staging system and a re-appraisal of prognosis and treatment. J Chronic Dis 1977; 30:277-305.
7. Feinstein AR. A clinical method for estimating the rate of growth of a cancer. Yale J Biol Med 1969; 41:422-33.
8. Charlson ME, Feinstein AR. A new clinical index of growth rate in the staging of breast cancer. Am J Med 1980; 69:527-36.
9. Wells CK, Stoller JK, Feinstein AR, Horwitz RI. Comorbid and clinical determinants of prognosis in endometrial cancer. Arch Intern Med 1984; 144:2004-9.
10. Boyd NF, Feinstein AR. Symptoms as an index of growth rates and prognosis in Hodgkin's disease. Clin Invest Med 1978; 1:25-31.
11. Boyd NF, Clemens JD, Feinstein AR. Pretherapeutic morbidity in the prognostic staging of acute leukemia. Arch Intern Med 1979; 139:324-8.
12. Feinstein AR, Pritchett JA, Schimpff CR. The epidemiology of cancer therapy. II. The clinical course: data, decisions, and temporal demarcations. Arch Intern Med 1969; 123:323-44.
13. *Idem.* The epidemiology of cancer therapy. III. The management of imperfect data. Arch Intern Med 1969; 123:448-61.
14. *Idem.* The epidemiology of cancer therapy. IV. The extraction of data from medical records. Arch Intern Med 1969; 123:571-90.
15. Feinstein AR. The problems of quantifying prognosis in lung cancer. In: Lane DJ, ed. Respiratory disease. London: William Heinemann, 1976:444-64.
16. Manual for staging cancer 1978. Chicago: American Joint Committee for Cancer Staging and End Results Reporting, 1978.
17. Hutchison GB, Shapiro S. Lead time gained by diagnostic screening for breast cancer. JNCI 1968; 41:665-73.
18. Feinleib M, Zelen M. Some pitfalls in the evaluation of screening programs. Arch Environ Health 1969; 19:412-5.
19. Ihde DC, Hansen HH. Staging procedures and prognostic factors in small cell carcinoma of the lung. In: Greco FA, Oldham RK, Bunn PA Jr, eds. Small cell lung cancer. New York: Grune & Stratton, 1981:261-83.
20. Simon MA. Causes of increased survival of patients with osteosarcoma: current controversies. J Bone Joint Surg [Am] 1984; 66:306-10.
21. Feinstein AR. On classifying cancers while treating patients. Arch Intern Med (in press).
22. *Idem.* Clinical epidemiology: the architecture of clinical research. Philadelphia: WB Saunders, 1985.
23. *Idem.* An additional basic science for clinical medicine. IV. The development of clinimetrics. Ann Intern Med 1983; 99:843-8.