Letters to the Editor

Prospective Multihospital Surveillance Studies—A Controversy

To the Editor:

Dr. Robert Haley's editorial, "The Vicissitudes of Prospective Multihospital Surveillance Studies" (June 1988, pp 228-231), is a critique of the Israeli Study of Surgical Infection.[1,2] The main difference between Dr. Haley's attitude and ours is that we concluded there is no alternative to the prospective approach for elucidating the multifactorial determinants of nosocomial infections, and that no serious interventions can be initiated without understanding these determinants.

The Israeli study reports a multihospital prospective study with the added dimension of comparing the outcome of patients in different hospitals as a function of different patient-management procedures. Although such studies may be difficult to perform, better and more rigorous prospective studies are needed to generate meaningful data for nosocomial infection research. We address issues in the design and the analysis of multihospital studies that have seldom been dealt with in the past: the necessary standardization of the data collection system, the uniform training of the nurse epidemiologists, the within-hospital heterogeneity in the rates of surgical infections, the possible bias introduced by length of hospitalization, and the problematic decision on the presence or absence of infection. The purpose of publishing the methodology paper was to initiate a constructive discussion on these methods and on the difficult problems that will always confront initiators of a study of this kind, but which are surmountable. Specific comments in the editorial are addressed below.

1. *Selection of hospitals.* The main purpose of the study was to use comparisons among hospitals to gain insight into how different hospitals manage surgical patients to understand why their observed infection rates vary so much. The selection of hospitals should be understood in this light. The number of institutions was secondary to the uniformity of the data collection. The purpose of the validation process was to demonstrate that infection rates and their possible determinants were measured with uniformity and accuracy that would justify interhospital comparisons. The main thrust of the study is therefore in its internal validity rather than its external validity (the applicability to all hospitals in Israel). The external validation of the study can be tested if similar multihospital prospective studies in other settings will employ the same standardized study methods.

The editorial mentions an effort made in the United States that included thousands of hospitals for the comparison of mortality rates[3] and that was not successful (editorial, p 228). Increasing the number of hospitals included in an analysis is no substitute for careful recording of the clinical course of patients and information about their management, nor for a validation process of the data collection system.

2. *Selection of patients and seasonal variation. The* season of the year was no different from any of the other potential confounders needing to be controlled for in order to estimate the residual effect of the hospital. The distribution in our data of the number of operations by type, season, and hospital ensure that the hospital and seasonal effects can be well separated for each major operation. Incidentally, seasonality did not have an unconfounded effect on surgical infections in hernia operations. This does not mean it will have no effect in other types of surgery and it certainly would have to be considered in all future analyses (as we demonstrated in the analysis of the second of the two articles). The editorial raises the possibility that different operations were performed in different seasons. This was not so in our study. The surgeons generally operated less in the summer and more during the other seasons, but that applied to all types of surgical procedures. The selection of operations by season is unlikely in any large general hospital, especially in this counntry where there are no specialized hospitals.

3. *Training of the nurses and the data collection system.* The nurses were all experienced nurse epidemiologists who agreed to participate in the study. They were trained as a group prior to its initiation. The training exercises consisted of solving problems in epidemiologic research adapted to hospital infection from those given at the Master of Public Health course in the School of Public Health, Jerusalem. Examples of such exercises included the meaning of rates, the implication of loss to follow-up in a prospective study, the reliability and validity of various signs and symptoms in the diagnosis of disease, and how these concepts affect the definitions of nosocomial infections.

It is true that the nurses were not "paid for their effort," but we refuse to accept that lack of payment would have had a detrimental effect on the diligence of these experienced, dedicated, and willing nurse epidemiologists. Also, hospital directors as well as the heads of sur-

https://doi.org/10.2307/30105103 Published online by Cambridge University Press

gical services and officials of the Ministry of Health actively participated in the project through its completion. This was not a regular surveillance, but rather a baseline information study. The high motivation of all ensured that the nurses were not detracted from their task.

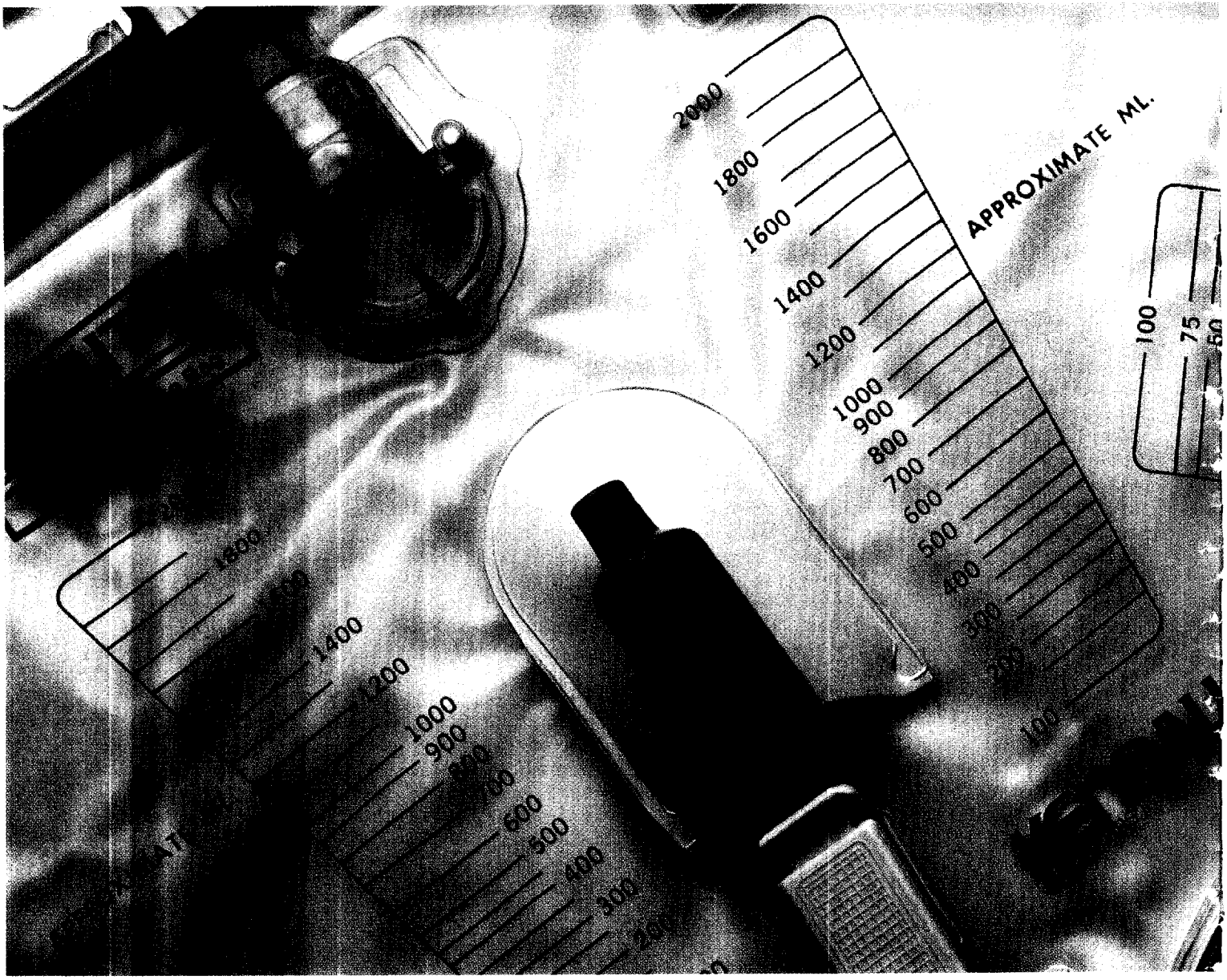
'The role of the two central team nurses (CTNs) continued beyond the standardization of the field nurses' work. They rotated continuously among the hospitals throughout the data collection period, monitoring the quality of information. For example, in order to evaluate the degree of coverage, they periodically reviewed the operating room records against the list of surgical patients that had been sent to the office. In addition, because the central team nurses spent half their time at the central office reviewing questionnaires, they were able to spot inconsistencies and systematic omissions and contact the appropriate hospital. As a result, the quality of the information did not decline as the study progressed, but actually improved. However, as previously discussed[1] we cannot prove this because we did not formally evaluate the nurses' compliance toward the end of the study. Of 11 hospitals, only 1 failed to complete the sample size and the postdischarge follow-up because the nurse left.

4. Diagnosis of wound infection. Diagnosis of wound infection was made by a panel of physicians after the patient was discharged. The decision on the presence or absence of infection was based on the nurse's daily log describing each wound (whether it developed a complication or not) as well as treatments received, and the laboratory tests performed. Evaluation of each patient's record was done without knowledge of the hospital involved. We do not agree that this method could increase the variability among the hospitals. On the contrary, the panel was unbiased in its decision in contrast to a local hospital team, which might have been. The nurses were trained to record what they saw but to avoid forming an opinion on the presence or absence of wound infection, thus promoting as objective an evaluation of the wound as possible.

Reaching agreement between panel members on what set of signs constituted an infection was important and required a formal evaluation. The kappa index of specific agreement between physicians was based on the panel of four, who reviewed the nurses' daily records. The physicians were not randomly sampled from some physician population. As a result we did not assume that the interphysician term is absent from the weighted kappa index (Fleiss 1981, Gross 1986), as suggested in the editorial. We know that the difference between the panel members' diagnoses reflects difference in interpreting the daily follow-up notes made by the nurse. Following the revision of the definition, the interobserver agreement was very high, an indication of general agreement among the participating physicians and not as a result of physician 2 reinterpreting the definition of pus correctly (see the shape of the graph in appendix 1, article 1). There is no way of knowing which physician was "right," and in any case the issue of being right relates to the validity rather than the reliability of the definition.

5. Definition of wound infection. In addition to the classic definition of "pus in the wound" we used a broadened second definition that included not only patients with pus, but also those with any continuous discharge on more than two days together with at least two of the following: systemic treatment with antibiotics, local treatment such as draining, and pure culture of the same pathogen on more than one occasion. The validity of the broadened definition was evaluated using prolongation of hospital stay as a criterion of morbidity Dr. Haley suggests that the only a priori hypothesis at issue here is whether the patients with infection added by the broader definition have a lower average prolongation of stay than those with wound infection defined by the presence of pus and that the statistical significance should have been evaluated using a one-tailed test. However, inspection of Table 6 in article 1 reveals that the average prolongation of stay for patients added by the broader definition was actually longer for three types of surgical procedures: colon, breast, and blood vessels. This suggests that the broader definition does not result in the misclassification of some uninfected patients among the infected ones. The misunderstanding here is very important. The use of "pus in the wound" is the long-sanctioned dogma for defining surgical infection. However, this definition almost certainly results in a lower-bound estimate of the "true" rate. Moreover, the presence of a discharge was an observable fact, whereas the nature of the discharge was a subjective evaluation. We therefore propose that in the absence of objective criteria for pus the second definition is better for a multihospital study.

6. Hospital discharge policy. The postdischarge follow-up of 1,000 patients in the Israeli study provided a unique opportunity to assess the possible bias introduced by the discharge policy on the interhospital comparisons. As was clearly stated in our discussion of the first article (p 238) we never dismissed the possibility that interhospital differences may have an effect (although it was not significant in the strict statistical sense) on the estimates of wound infection in the various hospitals. Rather, we emphasized that hospitals in Israel discharge patients relatively late, and as a result, the number of infections discovered at home was small and the corresponding rates not very stable. Larger samples of postdischarge patients are therefore needed to provide a more reliable estimate of the correlation between the average length of hospitalization and postdischarge infection rates. Furthermore, we are currently examining the effect of the length of hospitalization, not only on the rate of infections discovered after the patient has been discharged, but also on the risk estimates of various factors. We agree that further investigation of this issue will be needed before we can disregard length of hospital stay as



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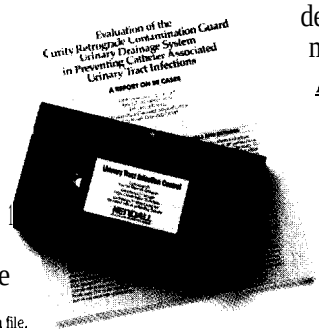

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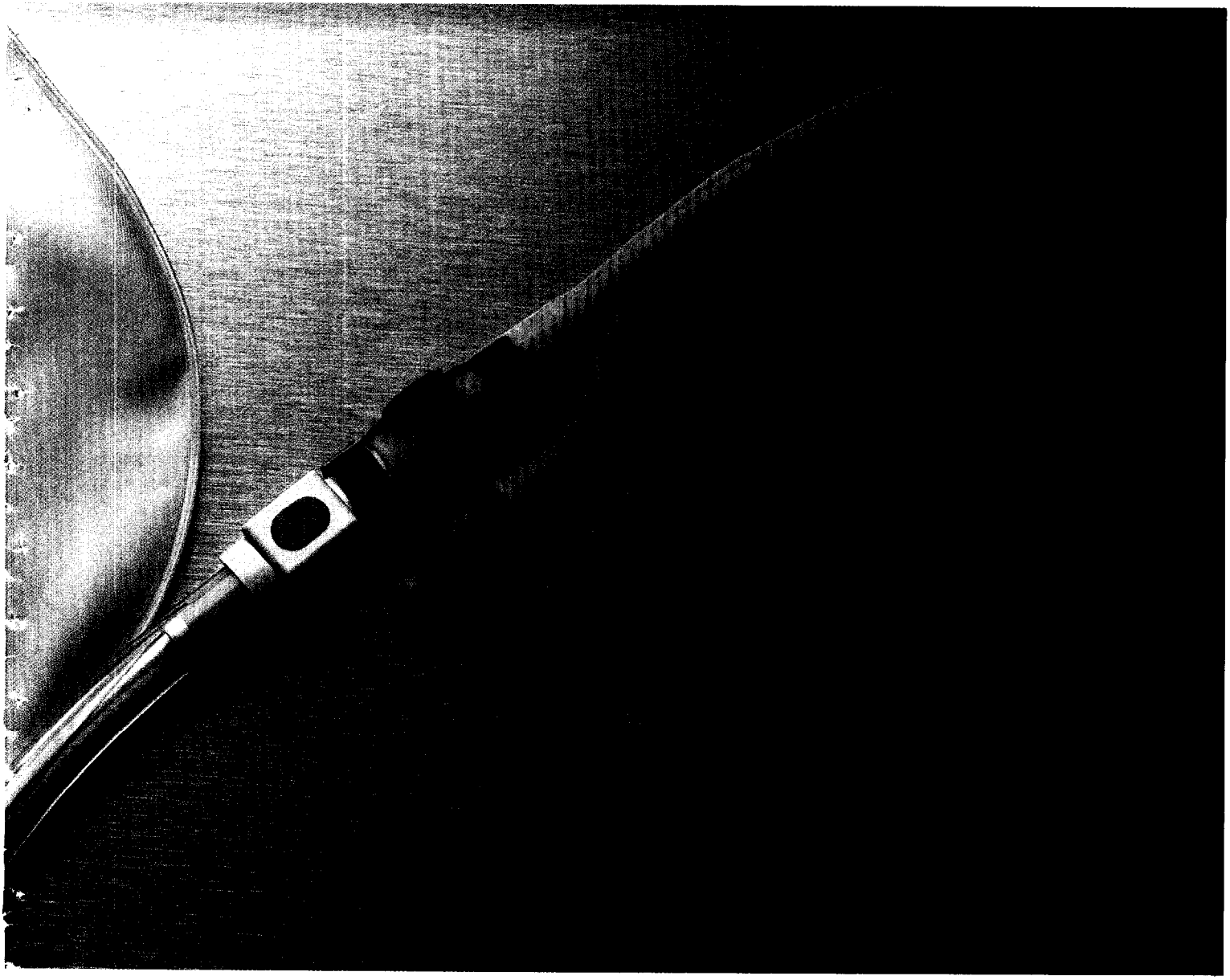

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a potential confounder for the interhospital comparisons.

7. Interhospital comparisons in article 2. In article 2 an attempt was made to isolate those determinants of the surgical wound infection rates that would explain the marked interhospital differences. Dr. Haley argues that this variability among the hospitals is probably explained by "differences in the sensitivity of the diagnoses of wound infection" in the various hospitals. This argument is extremely unlikely in view of the findings listed in Table 1 of the second paper: The same hospital, surveyed by the same nurse, was found to have a high infection rate in one type of operation relative to the other hospitals and a comparatively low rate in another. This variability was true in all the participating hospitals. This indicates that the same surgical teams may perform with varying degrees of success as far as wound infections are concerned in the various operations that involve different surgical techniques. This finding cannot be explained by one nurse diagnosing more infections than her counterpart in another hospital, as suggested by the editorial.

The use of drains in hernia operations was found to be the main risk factor for developing an infection. When adjusting for the effect of the four main risk factors in these operations, the differences among hospitals disappeared in all but two hospitals. The reasons behind the residual high risk in one hospital were discussed in the last paragraph of the Discussion in article 2. For the other hospital we could find no explanation.

As far as we know we never abandoned the interhospital comparisons in our second paper. The use of a model to separate the hospital effect from other risk factors is not a new technique. The finding that the hospital effect disappeared for 9 of the 11 hospitals after adjusting for the four main risk factors means that these factors contribute to the interhospital differences. Hospital comparisons were also made regarding the rate of use of drains, where marked differences were found controlling for the type of patient. This initiated a dialogue with the surgeons that resulted in initiating a clinical trial to evaluate the benefit of using drains in this type of surgery.

We would unreservedly agree with one of Dr. Haley's last statements that "no study is perfect" but would add the rider that "nor is any criticism."

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Elisheva Simchen, MD, MPH
Yohanan Wax, PhD
Mervyn Shapiro, MD
Theodore Sacks, MD

Oxacillin-Resistant *S aureus*

To the Editor:

What is the significance of *Staphylococcus aureus* cultures reported as resistant to oxacillin? The literature refers to methicillin-resistant S *aureus,* ie, MRSA.

Harry J. Silver, MD
Los Angeles, California

This question was referred to Peter N.R. Heseltine, MD.

Methicillin-resistant S *aureus* were first reported in Europe during the 1960s and are now an important cause of nosocomial cross-infections in patients hospitalized at tertiary care facilities in the United States. The only reliable therapy for such infections is vancomycin, which is both expensive and offers some potential for toxicity. There is some evidence that MRSA is spread from patients who are carriers of the organism (ie, asymptomatically colonized) to others: California has enacted some regulations regarding the transfer of MRSA culture-positive patients to skilled nursing facilities to minimize such transmission.

Oxacillin and nafcillin rather than methicillin are widely used in the United States by clinicians, and in response many laboratories now use oxacillin or nafcillin powder or disks to test the susceptibility of clinical isolates. (Methicillin susceptibility disks may also be more likely to deteriorate in storage than disks made from the other two antistaphylococcal penicillins.) MRSA are resistant to methicillin through intrinsic genetic mechanisms, rather than plasmid-mediated factors, which also render them resistant to most if not all beta-lactams, including other penicillins (eg, oxacillin and nafcillin) and most cephalosporins. The National Committee on Clinical Laboratory Standards (NCCLS) recommends that S *aureus* isolates that test resistant to methicillin or oxacillin or nafcillin be reported as resistant to all three agents. Because cephalosporin disk susceptibility tests of MRSA isolates do not correlate with clinical outcome, the NCCLS also recommends that MRSA be reported as resistant to cephalosporins. Thus, oxacillin-resistant S *aureus* must be considered equivalent to MRSA.

Peter N.R. Heseltine, MD
Associate Chairman of Medicine
Hospital Epidemiologist
Los Angeles County-USC
School of Medicine
Los Angeles, California

Correction

Two errors have been found in the article "Sample Size for Prospective and Retrospective Studies: The 2 × 2 Table" (Statistics for Hospital Epidemiology, December 1988). In the footnotes for Figures 1 and 2 (pp 564-565), "type II error" should read "type I error." Also, the title for Figure 2 should read: Sample size curves for *retrospective* studies. These figures are correctly discussed in the text (p 563). The authors and editors regret any inconveniennce the errors may have caused.