Perusing the Literature

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BRADFORD HILL HONORED

The October–December 1982 issue of *Statistics in Medicine* (Volume 1, Number 4) is dedicated to Sir Austin Bradford Hill, one of the fathers of controlled medical trials. In addition to reminiscences of Hill and discussions of his work and its influence on other investigators, the journal contains a bibliography of his English language publications. Papers included in this special issue that may be of particular interest to readers are the following:

Schoolman HM: The clinician and the statistician. Stat Med 1(4):311–316, 1982

Doll R: Clinical trials: Retrospect and prospect. Stat Med 1(4):337–344, 1982

Armitage P: The role of randomization in clinical trials. Stat Med 1(4):345–352, 1982

Fleiss JL: Multicentre clinical trials: Bradford Hill's contributions and some subsequent developments. Stat Med 1(4):353–359, 1982

Holland WW, Breeze E, Swan AV: Clinical trials: Some reflections. Stat Med 1(4):361–368, 1982

IMPLICATIONS OF CLINICAL TRIAL FINDINGS

A group of investigators have reported a benefit–cost analysis of application of their findings from a controlled clinical trial. The references for the current paper, the original report of trial findings, and the editorial which accompanied publication of the current paper are as follows:

Shapiro M, Schoenbaum SC, Tager IB, Munoz A, Polk BF: Benefit-cost analysis of antimicrobial prophylaxis in abdominal and vaginal hysterectomy. JAMA 249(10):1290–1294, 1983

Polk BF, Tager IB, Shapiro M, Goren-White B, Goldstein P, Schoenbaum SC: Randomised clinical trial of perioperative cefazolin in preventing infection after hysterectomy. Lancet 1:437–441, 1980

Scheckler WE: The cost of prevention: Common sense and decision trees. JAMA 249(10):1328, 1983

The investigators used a decision tree to determine excess costs of in-hospital and post-hospital morbidity for both treated and untreated patients. The benefit–cost analysis demonstrated that cefazolin, the drug found to be efficacious in preventing such morbidity in the clinical trial, was also cost-effective. The authors commented:

> The analysis has projected substantial savings were this prophylaxis regimen to be used universally. For other antimicrobials to be equally cost-effective, either

Controlled Clinical Trials 4:239–253 (1983)

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0197-2456/83/$03.00

they must be more efficacious or less expensive . . . The analysis indicates the importance of examining not just efficacy of a prophylactic antibiotic regimen but cost. The new cephalosporins may be quite effective at preventing post-hysterectomy infections, but this analysis indicates that even with substantially greater effectiveness than cefazolin they might not be equally cost-effective. Similarly, ampicillin, which is less expensive than cefazolin, could be equally cost-effective even if it were somewhat less efficacious.

This current report is recommended reading for those interested in evaluating the implications of implementing findings from clinical trials.

DRUG DEVELOPMENT AND EVALUATION

A series of articles that deals with detection of adverse drug reactions has been published recently:

Venning GR: Identification of adverse reactions to new drugs. I: What have been the important adverse reactions since thalidomide? Br Med J 286:199–202, 1983

Venning GR: Identification of adverse reactions to new drugs. II—How were 18 important adverse reactions discovered and with what delays? Br Med J 286:289–292, 1983

Venning GR: Identification of adverse reactions to new drugs. II (continued): How were 18 important adverse reactions discovered and with what delays? Br Med J 286:365–368, 1983

Venning GR: Identification of adverse reactions to new drugs. III: Alerting processes and early warning systems. Br Med J 286:458–460, 1983

Venning GR: Identification of adverse reactions to new drugs. IV—Verification of suspected adverse reactions. Br Med J 286:544–547, 1983

Venning surveyed ten British physicians and ten heads of drug regulatory authorities for their opinions on the most important adverse drug reactions determined since thalidomide. From the lists provided by the 20 respondents, a master list was compiled. Venning then examined the published reports of adverse reactions to these drugs in order to identify the first, which alerted attention to the adverse effect, and the subsequent reports, which confirmed the initial warning (since the possibility of false alerts makes verification essential). The author reviews the designs of the reported studies and provides criteria for evaluating the evidence provided by them. In the summary Venning comments that the delays in publication of alerting reports are minor in comparison with delays before verification of adverse reactions and action by regulatory agencies.

Two other investigators concerned with adverse drug reactions have described a study of post-marketing drug evaluation:

Borden EK, Lee JG: A methodologic study of post-marketing drug evaluation using a pharmacy-based approach. J Chronic Dis 35:803–816, 1982

These investigators were interested in developing a model that could be used for concurrent data collection on large groups of patients. In addition, the model had to be appropriate for both established and new drugs; the population to which the data applied had to be definable in such a way that both study participants and nonparticipants could be characterized; and health

events had to be completely reported, classified, and coded. As the authors noted, "At present, faced with a credible question of drug-induced adversity there are frequently no data from which to judge the magnitude of the problem or investigate for causal associations."

Borden and Lee enrolled patients through participating pharmacists by identifying patients who filled prescriptions for antibacterial agents. Patients were followed for 30 days after the initial prescription using a mail questionnaire and telephone follow-up when necessary. The investigators achieved questionnaire follow-up of 92.9% of the participants. Life/death status was determined for 97.9% of the participants. The authors noted that the approach they used required a sophisticated organizational structure to assure that the investigators from the various disciplines involved worked "in harmony." This reader found the approach described in this article appealing, not as a replacement for clinical trials as the authors suggested, but as a method for evaluating the impact of controlled drug trials on future patients, after trial findings have been reported.

A special supplement to *Neurology*, edited by R.H. Mattson and entitled "The design of clinical studies to assess the efficacy and toxicity of antiepileptic drugs," has been published. The following papers are included:

Smith DB, Escueta AVD, Cramer JA, Mattson RH: Historical perspective on the choice of antiepileptic drugs for the treatment of seizures in adults. Neurology 33(suppl 1):2–7, 1983

Escueta AVD, Mattson RH, Smith DB, Cramer JA, Collins JF: Principles in designing clinical trials for antiepileptic drugs. Neurology 33(suppl 1):8–13, 1983

Mattson RH, Cramer JA, Escueta AVD, Smith DB, Collins JF, VA Epilepsy Cooperative Study Group (Browne TR, Crill WE, Homan RW, Mayersdorf A, McCutchen CB, McNamara JO, Rosenthal NP, Treiman DM, Wilder BJ, Williamson PD, Young LM): A design for the prospective evaluation of the efficacy and toxicity of antiepileptic drugs in adults. Neurology 33(suppl 1):14–25, 1983

Cramer JA, Smith DB, Mattson RH, Escueta AVD, Collins JF, VA Epilepsy Cooperative Study Group (Browne TR, Crill WE, Homan RW, Mayersdorf A, McCutchen CB, McNamara JO, Rosenthal NP, Treiman DM, Wilder BJ, Williamson PD): A method of quantification for the evaluation of antiepileptic drug therapy. Neurology 33(suppl 1):26–37, 1983

Finally, a recent report on trends in new drug development may be of interest to some readers:

Wardell WM, May MS, Trimble AG: New drug development by United States pharmaceutical firms, with analyses of trends in the acquisition and origin of drug candidates, 1963–1979. Clin Pharmacol Ther 32(4):407–417, 1982

The authors give particular attention to the decline in self-originated new chemical entities brought to the stage of clinical testing by U.S.-owned companies in the period 1975 through 1979.

NOTES TO THE READER

Regular readers of this column may observe that the listing of publications that appears at the end of the current column has been divided into more classifications than previously. The revised classification scheme is intended

to facilitate review of references by readers with specific interests. In particular, reports of findings from controlled trials have been subdivided on the basis of the *intervention strategy under evaluation.* Trials in which more than one type of intervention were evaluated (e.g., a drug regimen and a surgical procedure in addition to the control intervention) are included under "Other Trials." Publications included in the category "Reports from Related Studies" are often reports from investigators involved in a specific trial but deal with questions other than comparison of findings for the randomized intervention groups.

As noted in earlier columns, the identification of articles for citation depends upon this writer's awareness of the published reports. Only a few journals are screened on a regular basis [see Controlled Clin Trials 2(4):327–333, 1981]. The references included in this report were derived from screening 246 separate issues of 35 different journals. All readers are not only invited but *encouraged* to send either preprints or reprints of recent publications or a letter or card to provide references for inclusion in future reviews.

Announcements

M.R.C. trial of multivitamin prophylaxis in pregnancies at risk of neural tube defects. Lancet 2:1412, 1982

Discussions and Critiques of Specific Trials

Isoniazid prevention of tuberculosis. Lancet 1:395–396, 1983

Recruiting for multicentre trials. Lancet 1:78, 1983

Senile disciform macular degeneration. Lancet 1:278–279, 1983

Treatment of multiple sclerosis. Lancet 1:909–910, 1983

The trial of homoeopathy. Lancet 1:108, 1983

Adler MW, Belsey EM, McCutchan JA, Mindel A: Should homosexuals be vaccinated against hepatitis B virus? Cost and benefit assessment. Br Med J 286:1621–1624, 1983

Allen ED: Laser photocoagulation of senile macular degeneration. Br Med J 286:1357–1358, 1983

Angell M: Multiple sclerosis and the Ingelfinger Rule. N Engl J Med 308(4):217–218, 1983

Barclay WR: BCG: An effective immunizing agent. JAMA 249(17):2376, 1983

Barnes G: A nurse's experience in the MRC's hypertension trial. Br Med J 285:1625–1627, 1982

Bernstein C: Alerting SMD victims in time. Sightsaving 51(2):16–21, 1982

Bird AC: Laser photocoagulation of senile macular degeneration. Br Med J 286:1001, 1983

Burch PRJ, Seltzer CC, Oster KA, Gordon DB, Walker WJ, Bross IDJ, Cutler JA: The Multiple Risk Factor Intervention Trial. JAMA 249(11):1435–1437, 1983

Clemens JD, Chuong JJH, Feinstein AR: The BCG controversy. A methodological and statistical reappraisal. JAMA 249(17):2362–2369, 1983

Findley LJ, Whelan DM, Moser KM: Long-term oxygen therapy in COPD. Chest 83(4):671–674, 1983

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Goldman KP, Valenzuela P, Galleguillos F, Empey DW, Festenstein F: Tuberculosis. Lancet 1:592–593, 1983

Gordon RS, Sanders WE: Implications of recent B-blocker clinical trials for patients after myocardial infarction. JAMA 249(18):2482–2483, 1983

Griffiss JM: Vaccination against meningococcal disease. N Engl J Med 308(23):1421, 1983

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Hanckel FS, Duff P, Polk BF, Shapiro M, Munoz A, Tager IB, Schoenbaum SC: Risk factors for infection after hysterectomy. N Engl J Med 308(21):1290–1291, 1983

Hart JT, Barley SL: Secondary prevention of myocardial infarction: An uncertain feeling. J R Coll Gen Pract 32:651–653, 1982

Kaplan NM: Therapy for mild hypertension: Toward a more balanced view. JAMA 249(3):365–367, 1983

Kennedy CO, Couzigou P, Richard-Mollard B, Fleury B, Amouretti A, Beraud C, Jenkins MD, Clover AM: Homoeopathy. Lancet 1:482, 1983

Lorber J: Vitamins to prevent neural tube defects. Lancet 2:1458–1459, 1982

McFarlin DE: Treatment of multiple sclerosis. N Engl J Med 308(4):215–217, 1983

Nixon PGF, Pugh S: Coronary artery bypass surgery. Lancet 1:242, 1983

Oslo Study Research Group, Leren P, Helgeland A, Hjermann I, Holme I: MRFIT and the Oslo Study. JAMA 249(7):893–894, 1983

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Zumoff B, Weinblatt E, Ruberman W: Mortality after myocardial infarction. JAMA 249(7):885, 1983

Methods

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