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SPECIAL ARTICLE

Current Standards in Reported Drug Trials

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FOR several years, the Department of Pharmacology at the University of Alberta has asked students, as part of a course in pharmacology, to carry out a critical evaluation of claims made in drug advertisements. Each student is given a recent advertisement which had been mailed to a local physician in the previous two or three months, and is asked to report on the validity of the evidence used to support the various claims made in the advertisement. The various pharmaceutical companies have been asked to provide the student with a list of reports which they consider best support their advertised use of the drug. The purpose of this program is to provide students with the opportunity to cultivate the ability to assess critically the claims for new drugs. An additional purpose has been to attempt the inculcation of a cautious attitude on the part of the students towards claims made for new drugs[1] and to the heavy advertising pressure in general that is directed toward physicians.[2, 3]

In recent years it has been suggested to the students that they follow the procedure outlined by Mahon and Daniel[3] in assessing the accuracy of reports of drug trials quoted in support of advertised claims. Briefly, the criteria suggested for the reliability of the results of a drug trial are:

(1) The presence of proper controls—either placebo or standard therapy (except where the disease is universally and rapidly fatal).

(2) Random allocation of treatment to each patient to eliminate physician bias in assigning therapy.

(3) Objective evaluation of the results—if possible on a "double-blind" basis.

(4) Statistical analysis to determine if the results could have happened by chance—a requirement implying that a sufficient number of patients must be studied.

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The problem most frequently encountered by the students is the general dearth of reports of clinical trials which approach these requirements, which leads them to give a "Scots verdict" (i.e. "not proven") for many claims. If the literature on a subject is extensive, there may be a problem of selecting which articles to read, a difficulty which has brought up questions about the editorial strictness of various journals, and whether there is a better chance of finding properly executed drug trials in certain journals than in others.[2]

We have therefore attempted to determine if the standards of reporting drug trials in Canada have improved since Mahon and Daniel[3] did their survey of *The Canadian Medical Association Journal* of 1956 to 1960, and have also compared the present status with that which prevails elsewhere. To accomplish the first of these objectives we extended the original study to the present by surveying all reports of drug trials (other than case reports) appearing in *The Canadian Medical Association Journal* from January 1961 to November 1967. For purposes of comparison, a similar survey was conducted on drug reports appearing in the *New England Journal of Medicine* for the five-year period 1963 to 1967. This journal was arbitrarily selected on the basis of our opinion that it is widely read and has a reasonably strict editorial policy. The analysis of individual reports was conducted in the same manner as in the original survey, that is, a stepwise consideration of the presence or absence of the requirements for a valid drug trial in the order listed above. When an article was found to be deficient in one of these criteria, the analysis was not carried further. This generated five groups of drug trials, in order of increasing rigour:

Group 1: No controls.

Group 2: Valid controls, but non-random allocation of therapy.

Group 3: Valid controls, random allocation, but assessment not objective.

Group 4: Valid controls, random allocation, objective assessment but no statistical analysis.

Group 5: Valid trials: all requirements present.

TABLE I.—EVALUATION OF DRUG TRIALS

	Canad. Med. Ass. J., 1956 - 60[3]	*Canad. Med. Ass. J., 1961 - 67*	*New Eng. J. Med., 1963 - 67*
Group 1	133 (65.5%)	147 (55.7%)	49 (47.5%)
Group 2	49 (24.0%)	55 (20.8%)	18 (17.5%)
Group 3	6 (3.0%)	12 (4.6%)	3 (3.0%)
Group 4	4 (2.0%)	8 (3.0%)	13 (12.5%)
Group 5	11 (5.5%)	42 (15.9%)	20 (19.5%)
Total	203	264	103

Reports involving fewer than four subjects were not included in these categories, but were considered to be "case reports" of toxicity or efficacy, and were recorded separately. Editorials or correspondence mentioning drugs are not included—only original articles.

Results of the survey of trials with four or more subjects are shown in Table I. A chi-square analysis shows that there has been a significant improvement ($P < 0.01$) in drug-trial reports appearing in *The Canadian Medical Association Journal* in recent years when comparison is made with the original study by Mahon and Daniel.[3] The main changes have been the publication of fewer uncontrolled trials (Group 1) and about three times as many trials as before which can be considered completely reliable on the basis of our criteria (Group 5). The *New England Journal of Medicine* in recent years is also significantly ($P < 0.01$ by χ^2) better than *The Canadian Medical Association Journal* during the same period. However, the difference is almost entirely due to the greater proportion of Group 4 reports in the *New England Journal of Medicine*. It seems to us to represent a peculiar lapse in editorial policy that the authors of these papers were not asked to provide statistical evaluation of otherwise well-performed studies, unless these papers report trials with too few patients to permit proper analysis, or else the authors believe that it was immediately obvious there was no effect of the therapy.

One can only speculate on the reasons for the improvement in drug reports appearing in *The Canadian Medical Association Journal*. More widespread recognition of the principles of proper evaluation, a more critical editorial policy and an increase in personnel doing research are all possibilities, although the last is most unlikely as a cause of the change since the number of drug reports has remained at about 40 per year throughout the whole 12-year period of the surveys. Another possibility that is very difficult to assess is the increase in "prestige" or excellence of *The Canadian Medical Association Journal* with a consequent willingness of more investigators to publish their better work in this journal.

TABLE II.—REPORTS INVOLVING FEWER THAN FOUR SUBJECTS

	Canad. Med. Ass. J., 1956 - 60	*Canad. Med. Ass. J., 1961 - 67*	*New Eng. J. Med., 1963 - 67*
Efficacy	39	26	36
Toxicity	54	81	25
Total	93	107	61

There is one aspect of the data for "special reports" (Table II) which is worthy of comment, namely the ratio of efficacy to toxicity reports. Reporting the occurrence of peculiar and infrequent toxicities is a necessary part of the long-term assessment of toxicities which may occur, and may therefore be considered valuable even if only a few cases are reported. However, reports of efficacy in fewer than four patients cannot be construed as valuable additions to the literature, since very few of the conditions treated fall into the category of "invariably fatal" or are too rare to permit collection of sufficient patients to make possible a statisically valid trial (only 4 of 26 "efficacy" reports in *The Canadian Medical Association Journal* between 1961 and 1967 were considered to be in the "rare" category). The ratio of "efficacy" to "toxicity" reports might therefore be an indication of the strictness of the editorial policy in refusing "efficacy" reports of doubtful usefulness. On this basis the recent editorial policy of *The Canadian Medical Association Journal* appears to be better than that of the *New England Journal of Medicine* ($P < 0.001$ by χ^2).

Summary Analysis of reports of drug trials reported in *The Canadian Medical Association Journal* for 1961 to 1967, and in *The New England Journal of Medicine* for 1963 to 1967, following the criteria of Mahon and Daniel, suggests that drug trial reporting in Canada has undergone improvement in recent years, and that present editorial selection in *The Canadian Medical Association Journal* is as good as or better than that in *The New England Journal of Medicine*.

Résumé Il ressort de l'analyse des rapports sur les essais de médicaments publiés dans le *Journal de l'Association médicale canadienne* de 1961 à 1967 et dans le *New England Journal of Medicine* de 1963 à 1967, d'après les critères de Mahon et Daniel, que le compte-rendu des essais de médicaments au Canada s'est nettement amélioré au cours des dernières annés et que la sélection de la rédaction dans le *Journal de l'Association médicale canadienne* est aussi bonne, sinon meilleure que dans le *New England Journal of Medicine*.

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