Marks HM (2007). James Angus Doull and the well-controlled common cold.

Cite as:

Marks HM (2007). James Angus Doull and the well-controlled common cold. JLL Bulletin: Commentaries on the history of treatment evaluation (www.jameslindlibrary.org).

In 1931, James Angus Doull (1889-1963) and his colleagues at the Johns Hopkins School of Hygiene and Public Health reported a study evaluating "the prophylactic value of ultra-violet light in acute upper respiratory disease." Three hundred and seventy three medical and public health students were divided "at random" into three unequal-sized groups. The first group was to receive one ultraviolet treatment per week; the second group received two treatments; and the remaining group served as controls (Doull et al. 1931).

Doull consulted Lowell J Reed, Professor of Biostatistics (see Fee 1987, p 138-146), about how best to allocate the participants:

> *The method used by Professor Reed was to represent each volunteer by a die. Thus 122 white dice represented group A; 66 red dice group B and 185 black dice group C. The dice were thoroughly mixed in a sampling machine known to be practically free from systematic error. They were then withdrawn from the bottom of the machine one at a time. The name of each volunteer was written on a card and the cards were arranged alphabetically. The first die drawn being black, indicated that the first individual on the list belonged to the control group; the next happened to be red and indicated that the second name belonged to group B, etc. (Doull et al. 1931, p 463).*

That Reed proposed using colored dice to produce a random allocation is not a great surprise. Reed's doctoral training was in mathematics, and before coming to Hopkins in 1918 he wrote mainly about mathematics and its applications in astronomy. Since the late nineteenth century, several prominent biometricians had experimented with using dice to emulate a random process (Pearson 1900; Greenwood and Candy 1911; Stigler 1991); and one of these biometricians, Major Greenwood, was a close friend of Raymond Pearl, who had recruited Reed to Hopkins. Explaining why Reed and Doull thought random allocation especially desirable for this particular study is more difficult, since there is little direct testimony on this point. What follows is an indirect but hopefully plausible account of the circumstances surrounding this study.

In 1928, Johns Hopkins University had received a five-year, $195,000 grant from the Chemical Foundation to study the common cold, a condition "that makes every working man lose 1.4 days of his working life and every woman 2.1 days of hers" (*Time* 1928). Named in honor of John J Abel, Hopkins' Professor of Pharmacology, the fund was used to finance laboratory, clinical and epidemiological studies in the schools of medicine and of public health. James Doull, Associate Professor of Epidemiology, was put in charge of the fund, and of designing the clinical studies (Report of the Dean 1928-1928, p 133; Gafafer 1933).

Doull had joined the Hopkins Hygiene Faculty in 1922, a year after receiving his doctorate there. With Wade Hampton Frost, Doull taught the required course in epidemiology.[1] Prior to his involvement with the Abel Fund, Doull's work was focused almost entirely on epidemiological studies of diphtheria.[2] His one previous involvement with a therapeutic problem was a poorly controlled study of the prophylactic uses of diphtheria antitoxin (Doull and Sandrige 1924). Like any physician, Doull was nonetheless aware that there was no shortage of methods for treating the common cold. Alongside an inexhaustable supply of patent medicines were treatments ranging from vitamins to vaccines to ultra-violet light (Cecil 1925, p 80-94; Hill and Clement 1929, p 72-122). As he observed:

> *I think that the public should know that we know nothing [about the prevention and treatment of colds] in order that they will cease to waste money on all kinds of nostrums; money by the way that might profitably be used to aid study of these conditions.*[3]

Doull's animus against drug company promotions was common among US academics at this time (Marks 1997). He contemplated an academic study of vaccines to offset commercial influence, as well as a study of ultraviolet light, for

which "results of a suggestive but far from conclusive nature" have been reported.[4] Whether for lack of time, resources or because studies of vaccines deemed at the time to have been "well-controlled" had already been done elsewhere (Ferguson et al. 1927; Brown 1932), only the study of ultraviolet light was pursued.

Cold studies in this period invariably relied on volunteers. A common concern was whether those who volunteered for treatment did so because they experienced lots of colds and "hope to receive benefit" from treatment (Colebrook 1929, p 4-5). Researchers used a variety of means to reassure themselves that experimental and control groups were comparable, ranging from assembling comparison groups by "drawing lots" (Colebrook 1929), sorting volunteer cards by sex and date of previous cold (Ferguson et al. 1927), and analysis using covariates in non-randomised groups (Brown 1932). That Doull used dice in this study was almost certainly due to Lowell Reed, who was both familiar with and interested in random processes (Sartwell 1976). However, Doull made clear in the 11 December 1929 report of the Committee on Common Cold that the mechanism used for allocation to treatment or control group must be impersonal:

> *In any such experiment it is obviously necessary to have two groups, each of sufficient size, one to receive irradiation and one to go without it, each being comparable to the other in every way which can be measured. [....] Each volunteer therefore was assigned to his group, as nearly as may be by chance. It follows that no interchanges [exchanges] are permissible as between the groups.*

In addition to assigning volunteers at random, Doull emphasized, as Colebrook (1929) had, "that every precaution be taken to have the reporting of colds be as complete in one group as in the other." Doull reminded the student volunteers that they must have "sufficient scientific interest in this experiment" to "report faithfully any respiratory disease" they experienced. To aid complete reporting, the students were divided into small groups and a "paid student assistant" appointed to survey each group three times a week for reports of respiratory symptoms, and to obtain a more detailed record of symptoms when students reported positively (Doull et al. 1931, p 468-469).

After a school year's worth of observation (35 weeks), the study was concluded. The results did not favor irradiation; if anything, the group receiving more than 10 treatments had slightly more colds than the control group. The published report was unusually detailed for the era in its reporting of study procedures (allocation, follow-up, dropouts, etc.) and in its analysis of the results. Detailed comparisons of the baseline health and demography of the two groups (age, gender, marital status, disease history, etc.) were provided as evidence of the success of the randomization procedure. Most interesting is an analysis of the severity of colds (Doull et al. 1931, p 468-469). While most symptoms occurred at comparable rates in the two groups, there were fewer cases of "secondary fever" [a fever occurring after day two] in the treatment group (23 vs. 36 cases). Such a difference, the authors reported, "would be expected about nine times in a hundred trials" (Doull et al. 1931, p 475), an observation on the statistical limits of a clinical trial which would not become usual for several decades to come.

In 1930, Doull left Johns Hopkins for Case Western Reserve School of Medicine in Cleveland. Although he never resorted again to Reed's dice, one can see the influence of his cold prevention research on the design and protocols of his later studies of pertussis vaccines, in particular the emphasis on the importance of controls and case follow-up (Marks 2006). In his pertussis studies, Doull relied on alternation, which in his view was sufficient to prevent bias in selecting which children would receive the vaccine (Doull et al. 1936). However, the actual allocations departed from this "ideal" somewhat: in one recruiting location, Doull used children whose parents refused inoculation as the controls, while at a later point in the study, he assigned the vaccine in a 2:1 ratio, with every third child serving as a control.

For Doull, as for many investigators in this period, alternation, slips of paper, or rolls of the dice were merely alternative mechanisms for taking treatment assignment out of the researcher's hands. Thus, for example, some studies that reported using random assignment (Diehl et al. 1938) had actually used alternation (Armitage 2002). Although concern about manipulation of treatment assignment schedules can be inferred from Bradford Hill's comments (Chalmers 2002) on the Medical Research Council's trial of serum treatment of pneumonia (Medical Research Council 1934), steps to conceal treatment allocations from clinicians and participants to prevent foreknowledge of upcoming assignments had not been developed. One important step along this path was the 1944 British Medical Research Council placebo-controlled trial of patulin for treating the common cold (Medical Research Council 1944). The trial was distinctive for its explicit efforts to conceal upcoming treatment allocations from both patients and medical personnel (Chalmers and Clarke 2004; Clarke 2004).

Doull's 1931 study is mainly of interest for shedding light on contemporary methodological sophistication at the Johns Hopkins School of Hygiene. By the mid-1930s, Doull's former colleagues made Hopkins an important center of methodological innovation in therapeutic research. Doull's emphasis on follow-up and reporting in therapeutic studies was shared by his friend and senior colleague, Wade Hampton Frost (Marks 2006; Chalmers 2006). Doull himself went on to a distinguished career in public health, served twice as president of the American Epidemiology Society, and he was involved in the early years of the World Health Organization. After 1940, his scientific and clinical work focused increasingly on leprosy where "he was instrumental in developing the first scientific method for determining the

effectiveness of chemotherapy in leprosy" (Obituary 1963). Once again, Doull turned to a Hopkins statistician, William Cochran, who assigned patients to one of six treatment groups using a table of random numbers (Doull 1954). Concealing allocation schedules that had been generated in this way would ultimately set the standard for present-day clinical research.

Acknowledgements
I am grateful to Iain Chalmers for alerting me to Doull's work, as well as for helpful comments and corrections on earlier drafts.

This *James Lind Library* commentary has been republished in the *Journal of the Royal Society of Medicine* 2008;101:517-519.

References

A. Manuscripts

John Jacob Abel papers, Alan Mason Chesney Archives, The Johns Hopkins Medical Institutions, Baltimore, MD.

James A Doull papers, MS C 46, National Library of Medicine, Bethesda, MD.

B. Published sources

Armitage P (2002). Randomisation and alternation: a note on Diehl et al. The James Lind Library (www.jameslindlibrary.org).

Brown WE (1932). Vaccine in the prevention of the common cold. An experiment. American Journal of Hygiene 15:36-63.

Cecil RL (1925). Colds. Cause, Treatment and Prevention. New York: D. Appleton & Co.

Chalmers I (2002). MRC Therapeutic Trials Committee's report on serum treatment of lobar pneumonia, BMJ 1934. In: The James Lind Library (www.jameslindlibrary.org).

Chalmers I (2006). Joseph Asbury Bell and the birth of randomized trials. The James Lind Library (www.jameslindlibrary.org).

Chalmers I, Clarke M (2004). Commentary: The 1944 patulin trial: the first properly controlled multicentre trial conducted under the aegis of the British Medical Research Council. International Journal of Epidemiology 23:253-260.

Clarke M (2004). The 1944 patulin trial of the British Medical Research Council: an example of how concerted common purpose can get reliable answers to important questions very quickly. The James Lind Library (www.jameslindlibrary.org).

Colebrook D (1929). Irradiation and Health, Medical Research Council Special Report No. 131, p 4-5, 12-13.

Diehl HS, Baker AB, Cowan DW (1938). Cold vaccines: an evaluation based on a controlled study. Journal of American Medical Association 111:1168-73.

Doull JA (1954). Clinical evaluation studies in lepromatous leprosy. First series: diasone (Diamidin, 4-4'-Diaminodi-phenyl sulfone, dihydrostreptomycin. International Journal of Leprosy 22: 377-402.

Doull JA, Sandrige RP (1924). Is the prophylactic use of diphtheria antitoxin justified. Public Health Reports 39:283-294.

Doull JA, Hardy M, Clark JH, Herman NB (1931). The effect of irradiation with ultra-violet light on the frequency of attacks of upper respiratory disease (common colds). American Journal of Hygiene 13:460-477.

Doull JA, Shibley GS, McClelland JE (1936). Active immunization against whooping cough. Interim Report of the Cleveland Experience. American Journal of Public Health 26:1097-1105.

Fee E (1987). Disease & discovery. A History of the Johns Hopkins School of Hygiene and Public Health, 1916-1939. Baltimore: Johns Hopkins University Press.

Ferguson FR, Davey AFC, Topley WWC (1927). The value of mixed vaccines in the prevention of the common cold. Journal of Hygiene 26:98-109, esp. 104-105.

Gafafer WM, Doull JA (1933). Stability of resistance to the common cold: with a check list of publications from the John J. Abel Fund for Research on the Common Cold. American Journal of Hygiene 18:712–26.

Greenwood M, Candy RH (1911). The fatality of fractures of the lower extremity and of lobar pneumonia. A study of hospital mortality rates. Journal of the Royal Statistical Society 74:398-405.

Hill L, Clement M (1929). Common colds. Causes and preventive measures. London: William Heinemann.

Marks HM (1997). The progress of experiment. Science and therapeutic reform in the United States, 1900-1990. New York: Cambridge University Press.

Marks HM (2006). The Kendrick-Eldering-(Frost) trials of pertussis vaccine. The James Lind Library (www.jameslindlibrary.org).

Obituary (1963). James Angus Doull (1889-1963). Journal of the American Medical Association 185:65.

Pearson K (1900). On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. London, Edinburgh and Dublin Philosophical Magazine and Journal of Science, 5th series 50:167-169.

Report of the Dean of the Medical Faculty, The Johns Hopkins University (1928-1929).

Sartwell PE (1976). Memoir on the Reed-Frost Epidemic Theory. American Journal of Epidemiology 103:138-140.

Stigler SM (1991). Stochastic simulation in the nineteenth century. Statistical Science 6: 89-97.

Time (1928). Cold hunting. 23 January, 11: 25.

Endnotes

1. Johns Hopkins School of Hygiene and Public Health, Catalogue and Announcement for 1922-1923, p 62-63.
2. James A Doull, List of Publications, James A Doull papers, Box 1.
3. James Doull to Herbert Goddard, November 15, 1929. John Jacob Abel papers.
4. Memo re Abel Fund for Research on the Common Cold, no date, John Jacob Abel papers.

Back

Home Contents