James Angus Doull and the well-controlled common cold

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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 ultra-violet treatment per week; the second group received two treatments; and the remaining group served as controls.[1]

Doull consulted Lowell J Reed, Professor of Biostatistics,[2] 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 They were then withdrawn from the bottom of the machine one at a time.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.'[1]

That Reed proposed using coloured 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;[3–5] 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'.[6] Named in honour 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.[7,8]

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.[9] Prior to his involvement with the Abel Fund, Doull's work was focused almost entirely on epidemiological studies of diphtheria.[10] His one previous involvement with a therapeutic problem was a poorly controlled study of the prophylactic uses of diphtheria antitoxin.[11] 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 ultraviolet light.[12,13] 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.'[14]

Doull's animus against drug company promotions was common among US academics at this time.[15] 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.[16] 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,[17,18] 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.[19] Researchers used a variety of means to reassure themselves that experimental and control groups were comparable, ranging from assembling comparison groups by 'drawing lots',[19] sorting volunteer cards by sex and date of previous cold,[17] and analysis using covariates in non-randomized groups.[18] That Doull used dice in this study was almost certainly due to Lowell Reed, who was both familiar with and interested in random processes.[20] 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 had,[19] '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.[1]

After a school year's worth of observation (35 weeks), the study was concluded. The results did not favour 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.[1] 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 versus 36 cases). Such a difference, the authors reported, 'would be expected about nine times in a hundred trials',[1] 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 again resorted 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.[21] 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.[22] 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[23] had actually used alternation.[24] Although concern about manipulation of treatment assignment schedules can be inferred from Bradford Hill's comments[25] on the Medical Research Council's trial of serum treatment of pneumonia,[26] 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.[27] The trial was distinctive for its explicit efforts to conceal upcoming treatment allocations from both patients and medical personnel.[28,29]

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 centre 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.[21,30] Doull himself went on to a distinguished career in public health, served twice as president of the American Epidemiology Society, and 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'.[31] 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.[32] Concealing allocation schedules that had been generated in this way would ultimately set the standard for present-day clinical research.

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However, the significant careers advice that abounds concerning specialties can often be ignored by those meant to benefit – thus it should be encouraged that students should mould an investigative mindset that underpins success.

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DECLARATIONS

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None declared

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Confusion in equal measure

Sir,

With successive ocular oscillations I was able to visually partake in your scripted correspondence which you had consensually contributed to the *JRSM*.[1] It was only by this due process, and not, I hasten to add, by any other assimilated or subjunctive discursions [sic], that I am both rendered and obligated (here and now, that is, in this present moment of time) to concur and unconditionally agree with your stated and assumed viewpoint. Your avowed, declared and affirmed stance is admirable – and I am minded to assume a positive, and thus non-negative, psyche which is in turn positive (and thus non-negative) in both willpower and essence. That said, one must remember, that I should not publicly nor openly state these assertions. We know that overt is superior to covert, but equally it then surely is by the same token akin to the pouch of Douglas in your own profession: what lurks therein should by definition lurk. To be seen to be not lurking implies a measure of dissimilitude, and this leads to a lack of perspective.

Elaboration evaporates to a greater sense of overdoing. And the result? Well, failure of course. Just as the sun should never set on a breech, then too much exaggeration leads to the greater folly. The folly of Lord Darzi's attempt at evidence-based medicine. To gain a foothold in such arguments is to clutch at random ideas which float, ballpark-figure-like, in an imaginary delusional ether.

My point is thus: it is to realize that this letter will be of greater worth but, surely, lesser by dint of its certain context. My approach in such matters is but surely akin to that of your own.

In shared and mutual confusion,
Yours etc,

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DECLARATIONS

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None declared

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Prognosis: medical magic

I was surprised that Dr Sokol's essay on medicine and magic did not mention the soothsaying activity of doctors.[1] Prophesying clinical outcome is an everyday medical activity but this relies heavily on mathematical probability. To the patient, a doctor who can foretell the future may appear to have the charisma of the magician but today most patients believe that our predictions are based on solid scientific facts. Our diagnostic skills are derived from our observations of the attributes of a disease, without necessarily identifying the cause. In fact, with the exception of diseases related to micro organisms, aetiology is a mystery around which we elaborate unproven hypotheses. Herein lies the magic of medical practice. We operate not by sleight of hand but by sleight of word. Prophesying leans heavily on historic non intervention but our ethic is to treat according to the acquired knowledge within our own speciality. Characteristically we do not recommend placebos to cancer patients as alternatives to chemotherapy. Prognosis could be seen to offer the patient either a stick or a carrot. Without treatment, 'you will die'. With treatment, 'you may live a bit longer'. We bolster our beliefs when, with treatment, the patient survives beyond that arbitrary deadline. What if, after a period of reflection, the patient defies the witchdoctor and goes it alone? Do we continue to review that patient in outpatients knowing that management, with their eye on the purse, see these follow-ups as loss leaders? Do these loners fall into the sympathetic laps of the nurse-specialist or practice nurse? The 'sympathetic' but devious medical alternative might be to continue to see the patient, except privately. If the patient changes their mind we will probably change the prognosis for the worse. How often have we seen our prognostications and those of others turned on their heads? Patients' choice may be influenced by our messianic fervour to treat and their lack of medical literacy.[2] Prognosis carries a mystical/magical power of prediction and is all too easily used as leverage. The magician performs his trick and deceives us. Doctors merely deceive themselves.

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DECLARATIONS

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None declared

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Erratum

The authors of the paper 'Zabdiel Boylston's evaluation of inoculation against smallpox' (*JRSM* 2008;**101**:476–7)[1] are Arthur Boylston and AE Williams.

The author of the paper 'James Angus Doull and the well-controlled common cold' (*JRSM* 2008;**101**:517–19)[2] is Harry M Marks.

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