The Royal Society of Medicine

Journal of the Royal Society of Medicine; 2020, Vol. 113(1) 28–38
DOI: 10.1177/0141076819896274

Donald Mainland: anatomist, educator, thinker, medical statistician, trialist, rheumatologist

Doug Altman
Centre for Statistics in Medicine, University of Oxford, Botnar Research Centre, Oxford OX3 7LD, UK
Note: The author sadly passed away last year.

Introduction

Donald Mainland described himself as someone who started teaching as an undergraduate demonstrator in anatomy and continued trying to teach, orally or in writing, for the next 48 years.[1]

Mainland had a unique career. He graduated in medicine from Edinburgh in 1925 and spent 20 years as Professor of Anatomy in Halifax, Nova Scotia. From the early 1930s, he developed a remarkable grasp of statistical principles and methods, and in the second part of his career, he was Professor of Medical Statistics at the New York University. Here, his main focus was obtaining reliable estimates of the effect of health interventions in rheumatology. How did the remarkable transformation from anatomist to statistician come about?

Unusually, Donald Mainland dropped many autobiographical notes into his writings, so we know a lot about his motivations. For example, in 1954 he wrote:

> The remarks are those of one who, after graduating in medicine, started research on the embryology of the ferret. He was puzzled by error in cell measurement, by variations in the counts of chromatin particles, and especially by the problems of small samples, because ferrets were expensive. He obtained no answer from biologists, chemists, physicists, or mathematicians, until he was led to the solution by Dr. C. H. Goulden, an agricultural experimenter in Winnipeg, who introduced him to the book by R. A. Fisher (now Sir Ronald Fisher) on Statistical methods for research workers which had appeared three years previously (in 1925).

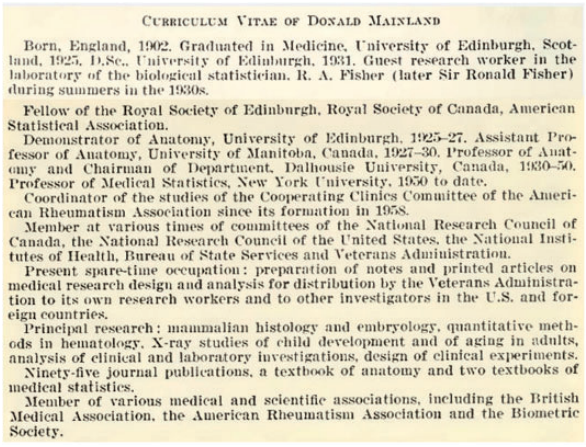
He then saw that the methods prescribed by Fisher for avoiding bias and allowing for chance, experimental error, biological variation and sample size were applicable in all fields of medicine, and that in his own field, anatomy, normal variations in nerve pattern, positions of abdominal viscera and other organs had often greater clinical importance than the so-called 'averages' that he had learned and was teaching. He stole time from the contemplation of the 15 arteries, which (in those days, at least) arose from the hypogastric artery, and spent this time in applying statistics to his own research and the researches of others, some of it during vacations in Fisher's laboratory. Then, after World War II, he realised that he could not run an anatomy department and keep abreast of statistical developments, and he chose the latter effort.[2]

He made rather similar remarks in one of his last publications, in 1980.[1]

Brief biography

Donald Mainland graduated in medicine at Edinburgh. He taught anatomy in Edinburgh and received a Doctor of Science degree there for his research in embryology and histology. In 1927, he moved to Winnipeg, Manitoba, Canada, and in 1930, at the age of 28, became Professor and Chairman of the Department of Anatomy at Dalhousie University. Even his earliest publications showed an interest in measurement issues, and foreshadowed an increasing interest in statistics. In 1938, he published his first book on statistics in medicine.[3] In 1950, he became Professor of Medical Statistics at the New York University and shortly afterwards published his best known book, *Elementary Medical Statistics*.[4] Thereafter, Mainland was a prolific and influential writer on statistical topics.

Mainland provided his own CV in the report of some Congressional hearings in 1967, of which more below.[5]



CURRICULUM VITAE OF DONALD MAINLAND

Born, England, 1902. Graduated in Medicine, University of Edinburgh, Scotland, 1925. D.Sc., University of Edinburgh, 1931. Guest research worker in the laboratory of the biological statistician, R. A. Fisher (later Sir Ronald Fisher) during summers in the 1930s.

Fellow of the Royal Society of Edinburgh, Royal Society of Canada, American Statistical Association.

Demonstrator of Anatomy, University of Edinburgh, 1925–27. Assistant Professor of Anatomy, University of Manitoba, Canada, 1927–30. Professor of Anatomy and Chairman of Department, Dalhousie University, Canada, 1930–50. Professor of Medical Statistics, New York University, 1950 to date.

Coordinator of the studies of the Cooperating Clinics Committee of the American Rheumatism Association since its formation in 1958.

Member at various times of committees of the National Research Council of Canada, the National Research Council of the United States, the National Institutes of Health, Bureau of State Services and Veterans Administration.

Present spare-time occupation: preparation of notes and printed articles on medical research design and analysis for distribution by the Veterans Administration to its own research workers and to other investigators in the U.S. and foreign countries.

Principal research: mammalian histology and embryology, quantitative methods in hematology, X-ray studies of child development and of aging in adults, analysis of clinical and laboratory investigations, design of clinical experiments.

Ninety-five journal publications, a textbook of anatomy and two textbooks of medical statistics.

Member of various medical and scientific associations, including the British Medical Association, the American Rheumatism Association and the Biometric Society.

Assistant Professor in Anatomy, University of Manitoba, Winnipeg

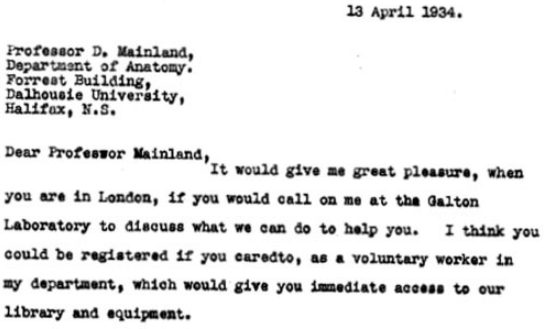
In 1927, Mainland moved to Winnipeg in Canada; his writings do not provide any specific motivation for this move. His three years in Winnipeg yielded 13 published research papers from 1927 to 1931. Five were related to ferrets and one to dogs. One article, in German, was a technical note on staining brains. The jump from this area of work to medical statistics is astonishing. Yet, as early as 1931, he began a paper on the sizes of nuclei in ovarian stroma with the following remarks:

> In histology two main routes of advance are open. The first is the change and improvement of preparation, fixation, and staining of tissues. The second, less used route is the application of strict quantitative methods to specimens prepared by ordinary technique. This second method has to its disadvantage great laboriousness, the natural antipathy of many toward mathematical methods, and the distrust with which statistical methods especially are viewed. On the other hand, this method is technically simple, consisting chiefly of careful measurement. The statistical treatment of the data may be mastered without great difficulty, and the distrust of statistics diminishes as one becomes familiar with the principles.[48]

Even by 1931, therefore, he had clearly recognised the importance of quantitative methods.

Professor of Anatomy, Dalhousie University, Halifax, Canada

In 1930, Mainland moved to be Professor of Anatomy at Dalhousie University, at the age of 28. Some of his early publications after moving to Halifax showed a concern about measurement issues, which undoubtedly led to his rapidly developing interest in statistics.[49] Mainland had been introduced to the writings of RA Fisher while in Winnipeg, just a few years after Fisher published his famous book *Design of Experiments*. It is clear that Mainland immediately saw the value of this methodology for his own research. Not only did he employ and write about random sampling from an early date, he visited Fisher more than once in London in summers in the 1930s. Those visits presumably followed Fisher's 1934 invitation:



13 April 1934.

Professor D. Mainland,
Department of Anatomy.
Forrest Building,
Dalhousie University,
Halifax, N.S.

Dear Professor Mainland, It would give me great pleasure, when you are in London, if you would call on me at the Galton Laboratory to discuss what we can do to help you. I think you could be registered if you caredto, as a voluntary worker in my department, which would give you immediate access to our library and equipment.

(Source: Fisher archive, Adelaide).

Fisher is better known for his theoretical developments (in statistics and genetics) than in relation to practical applications of statistics, so Mainland's observations about one of his visits are revealing:

> I recall that, during a summer that I spent as a guest in Fisher's laboratory in London, I saw the testing of human olfactory sense, the sampling of human hair, and an investigation of snails. Through personal contact with Fisher I came to know his common-sense attitude in practical research situations, and a desire to find a solution for the experimenter's problem, rather than to use the problem for the indulgence of his mathematical interests.[6]

In 1938, Mainland published his first book on statistics in medicine, *The Treatment of Clinical and Laboratory Data: An Introduction to Statistical Ideas and Methods for Medical and Dental Workers*.[3] Fisher was thanked profusely in the preface.

Mainland's 1938 textbook is unusual in its prominent treatment of laboratory data, clearly reflecting Mainland's unusual path into medical statistics. This emphasis is shown in particular by the 75-page chapter on 'Data based on measurements' and a further 37 pages on 'Errors in measurement'. Key ideas include concern about sampling variation, bias and problems associated with small samples.

Another unusual feature was the final chapter 'Publication of Data and Results'. Here he first discussed the over-summarisation of data in published research papers, and the desirability of others having access to the raw data. He observed that:

> Careful examination of many published articles reveals, however, that, in spite of their containing much numerical information, they do little more than present: (a) an author's opinions, and (b) data that seem to confirm those opinions, that is, do not disagree with them.

Among other topics he addressed in supplementary notes were several issues relating to sample size, including 'The size of sample necessary to demonstrate a significant difference' and 'The size of sample necessary to estimate a possible difference within desired limits' (pp. 305–308). Here he was thinking along lines much as we do now, although the ad hoc trial and error approaches he suggested at that time have been superseded, including in Mainland's later writings.

Later, Mainland was hugely impressed by the work of Bradford Hill, as exemplified by the 1948 report of the MRC streptomycin trial, which he described as 'a beacon'.[7] As he wrote in 1980 (quoted above), the opportunity to work on clinical trials was a major reason for his move from Halifax to New York in 1950. As he reminisced much later:

> ...the randomized controlled trial...is now so familiar as to have lost its glamour, but in the thirties and forties it was tremendously exciting to apply the new methods to research in histology, embryology, blood counts, cell measurement, and my radiological bone and joint studies.[1]

Mainland was largely self-taught as a statistician, which certainly put him apart from most academic statisticians. Fisher, not noted for his tolerance, clearly saw something in him. He appears to have remained in contact with Fisher, who wrote to Mainland as 'My Dear Donald' in 1955. Mainland was conscious of his unorthodox entry into the profession. He began a nice essay in 1950:

> A discussion of statistical methods in clinical research by one who is neither a professional statistician nor a clinician must appear rather incongruous. There may be some advantages in this incongruity, however, for there may be something of interest in the point of view of one who is using statistical methods daily in the laboratory and who is also in daily contact with clinicians. Such a person sees, by contrast, the difficulties of clinical research, and he sees how clinicians who possess keenly critical minds and are interested in scientific medicine are handicapped by lack of acquaintance with statistical ideas.[8]

Similar comments appear elsewhere in his writings.

Donald Mainland – Source: D. Mainland [photograph]. Dalhousie University Photographic Collection (PC1, Box 60, Folder 65). Dalhousie University Archives, Halifax, Nova Scotia, Canada.

Between 1939 and 1946, Mainland published only two journal articles. However, it is surely relevant that in 1945 he published his 863-page textbook on anatomy. After the 1938 book, he did not produce another statistical publication until 1948, when a 166-page journal article 'Statistical methods in medical research. I. qualitative statistics (enumeration data)', in effect, a mini textbook, appeared.[9] Whether this was intended as the first of a series is unclear, but only one further item appeared under this heading: part II, on sample size, appeared five years later and was only 11 pages.[10]

Mainland's 1952 text *Elementary Medical Statistics*,[4] although published when he was already in New York, was almost wholly written when he was

in Halifax. Indeed, he notes it was based on courses run in Dalhousie. It includes numerous uses of 'random' and 'randomize(d)', but none of 'random allocation', presumably reflecting the fact that while in Halifax he had little or no involvement in clinical trials. There is no doubt that Mainland had strong views on the importance of both random sampling and random allocation.

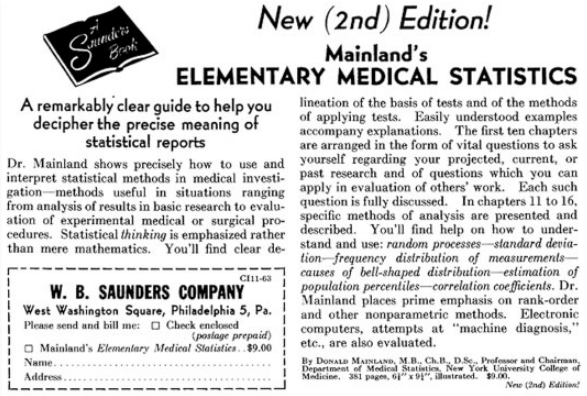
Professor of Medical Statistics, New York University: Rheumatology trials

The unique switch from Professor of Anatomy to Professor of Medical Statistics came just two years after the publication of his huge textbook on anatomy in 1948. It is clear that his earliest work in anatomy sparked his interest in measurements and things statistical, and this book was the watershed between his two very different careers. Just two years later, he effectively abandoned anatomy for medical statistics and, in particular, clinical trials. A revealing comment is from 1980:

> The possibility of promoting controlled trials in medicine was one of the inducements for me to become a medical statistician in New York in 1950. In those days many clinical and laboratory investigators expected a statistician, after a brief consultation, to do some arithmetic and affix a 'certificate of purity' to their reports. Others, who wanted a statistician to co-operate from the planning stage onwards, often failed to realise how few projects a single statistician could thus handle simultaneously . . . Fortunately, I was able to escape into full-time participation in multicentre therapeutic trials in rheumatology, in which I could visit the clinics and get to know the investigators. Here, as in anatomy teaching, a medical degree (along with my radiological research) gave me insight and entrée, and I even acquired a third label – 'rheumatologist'.[1]

Clearly, he relished the new opportunities. Although he was an author of rather few published reports of clinical trials, it seems he was deeply involved in the trials programme. In 1954, he wrote memorably: 'To omit randomization because one cannot see clearly how bias could occur is like trusting that glassware in chemistry is clean because it does not look dirty'.[11] Mainland was in the Department of Preventive Medicine at New York University, but it seems that most of his clinical projects were in the field of rheumatology.

A clear shift of emphasis can be seen when comparing the two editions of his Elementary Medical Statistics.[4,12] The second edition, written after many years in New York, is so different from the first it may fairly be considered a different book. The first 10 chapters in the second edition are written in question and answer format. Unusually, this section includes a chapter on 'Lost information' (what we now call 'missing data').



Educational writings about medical statistics

Mainland's unique contribution was a long series of writings aimed at explaining and discussing statistical ideas for non-experts. As well as his textbooks, he published many educational articles. For example, early in his time in New York, he wrote 14 chapters in a volume of *Methods in Medical Research* (with co-authors for a few chapters)[13] and an article about the problems of being a medical statistician.[2] He wrote about the use of case records, including how to do non-randomised studies well,[14] and he published three articles in the *American Heart Journal* titled 'Notes on the planning and evaluation of research, with examples from cardiovascular investigations', a total of 39 journal pages.[15–17] These were soon followed by two articles on 'The use and misuse of statistics in medical publications'[18] and 'The clinical trial – some difficulties and suggestions'.[19]

Most notable, however, were three series of privately circulated 'notes'. First, between August 1959 and September 1966, he produced a long series of 145 Notes from a Laboratory of Medical Statistics. As Mainland later observed[20]: 'The 2,500-name mailing list included persons in all areas of medicine and related disciplines, and 25 countries were represented'. The series continued under the auspices of the Veterans Administration – 104 items from July 1967 to December 1970 – with a new title, Notes on Biometry in Medical Research. Simultaneously, between January 1967 and December 1969, Mainland produced Statistical Ward Rounds as a

series of 18 long articles in the journal *Clinical Pharmacology and Therapeutics*. These publications together form a substantial body of work – in reprinted book form, they comprise 1912 pages.[21–23] At the end of the first of the Ward Rounds, he outlined his motivation:

> I have to confess that my deepest reason for starting these ward rounds is that I enjoy trying to get my thoughts clearer about statistical ideas and methods, bringing old ideas to new problems, and looking at old problems in new ways.

The Notes were often a test bed for new educational material. Later journal articles often drew on the material in the Notes. The first 10 items in the series Notes from a Laboratory of Medical Statistics were, however, based on the three articles he had published in the *American Heart Journal*, and this material then became the basis of the first 10 chapters of the second edition of his book *Elementary Medical Statistics*.[12] Most of the Notes addressed issues that arise frequently in everyday applications of statistics, such as sample size, the meaning of statistical significance, multiple testing, causal inference and identifying outliers.

Not only was Mainland highly prolific, he was influential. As Alvan Feinstein wrote: 'With his textbook . . . and his many other writings, he has probably contributed as much as any single person to the statistical sensibility of clinical investigators in North America'.[24] Even 25 years after his death and about a half-century after its publication, an editorialist in the *Journal of Rheumatology* recommended Mainland's Elementary Medical Statistics 'to all young clinician scientists'.[25]

Statistical thinking

A recurring theme of Mainland's writings was the importance of clear thinking about the problem rather than focusing on the mathematical side of statistics. This idea is the title of a 1982 article, 'Medical statistics – thinking vs. arithmetic',[26] but 30 years earlier, he had addressed the same idea in the opening sentence of the Preface to his text *Elementary Medical Statistics*:[4]

> Those who have for many years stressed the importance of statistical thinking in medicine cannot be entirely happy to see statistics becoming established as a subject in the undergraduate curriculum, for it thereby becomes liable to the curse that is on all medical 'subjects': the emphasis on memorization, on techniques, and on preparation for board examinations which foster statistical pedagogy.

Similarly,

> Research workers' widespread lack of understanding of the rationale of statistical techniques, and the frequent use of statistical tests as a substitute for thoughtful investigational design, meticulous work, and repetition of experiments, justify the antagonism to statistics exhibited by some experimenters. To one who has had personal experience of the way in which statistical thinking, as distinct from statistical arithmetic, can promote good investigation, this perversion of statistics is lamentable.[18]

Such thinking has its roots in Mainland's earliest statistical work, as exemplified by this comment from 1936: 'What is required in clinical work is not elaborate mathematical tests, but an understanding of the meaning of chance, and adequate precautions that the samples, however small, are unbiased'.[27]

In 1929, Dunn had reported that over 90% of 200 journal articles required statistical methods but had not used them, and that, in almost 40%, conclusions were drawn which could not have been proved without setting up some adequate statistical control.[28] Dunn felt that about half of the papers should never have been published as they stood. Mainland commented on Dunn's study and noted that his own survey of clinical journals

> . . . revealed the same general verdict, perhaps even a more adverse one, was appropriate in the clinical field . . . Frequently, indeed, the way in which the observations were planned must have made it impossible for the observer to form a valid estimate of the error . . . an idea of what results might be expected if the experiment were repeated under the same conditions. (Mainland,[3] p. 5)

He recognised that many errors are elementary:

> Since medicine is so quantitative we might expect that practitioners would avoid at least the simpler mistakes in dealing with counts and measurements, but almost any volume of a medical journal contains faults that can be detected by first-year students after only three or four hours' guidance in the scrutiny of reports.[4]

In Note 12 of Notes on Biometry in Medical Research,[21] Mainland discussed in detail the findings

of an important review of publications by Schor and Karten.[29]

Poor reporting of research has become a major concern only rather recently.[28] So Mainland's 1938 textbook was unusual in concluding with a whole chapter on 'Publication of data and results'. In the first paragraph, he observed that: '... incompleteness of evidence is not merely a failure to satisfy a few highly critical readers. It not infrequently makes the data that are presented of little or no value'.[3]

Tests of significance

Mainland was well aware of difficulties relating to the wide use and misinterpretation of significance tests and their resulting *P* values. Of particular concern, then as now, was the wide misinterpretation of a result that was not statistically significant ($P > 0.05$) as evidence of 'no effect'. In 1963, he wrote:

> The terminology itself is, I think, largely to blame for the persistent confusion. Our thinking today might have been much clearer if from the beginning the statisticians had used a more specific, more explanatory, and less pretentious term such as 'random frequency test' instead of the ambiguous and grandiloquent 'significance test'.[12]

He did use the term 'random frequency test' in some of his writings, including in his last publication[30] although not in his contemporaneous textbook.[31] His suggestion had no impact. Mainland recognised the importance of confidence intervals, describing these as early as 1948.[9] Again, he observed that their naming was unfortunate:

> ... as one of my students remarked, they might be more appropriately called 'no confidence limits'. Perhaps a still better title would be 'minimal estimates of ignorance'. This sounds discouraging, but it forces us to recognize that no single study can give us very precise knowledge of the value of a therapy.[12]

He does not seem to have suggested the abolition of *P* values even though he clearly saw their problems:

> Statistical tests are very dangerous drugs.[32]
> Compulsion to apply a random frequency [significance] test may arise from ignorance or from tribal custom. (Mainland,[21] p. 77)

This perspective was clearly an important element in his widely stated promotion of statistical thinking rather than statistical arithmetic.[26]

Insights

Donald Mainland was not a methodological innovator. Although a method of analysing crossover trials is dubbed the Mainland-Gart test, it is not much used these days. Rather, Mainland addressed common situations in clinical research for which he often demonstrated unusual insights, in some instances many years before the concepts became well-recognised. Some notable examples follow.

Confidence intervals

Confidence intervals were introduced in the 1930s,[33] but they did not become common in clinical research until the 1980s. Mainland may first have described them in his 1948 mini-text on the analysis of categorical ('enumeration' data).[9] In both editions of his textbook *Elementary Medical Statistics* (1952 and 1963), confidence intervals were introduced before tests of significance. In the first edition he wrote: 'Confidence intervals are required for all estimates, whether of enumeration data or measurements; and they always refer to populations that could be randomly represented by the observed sample' (Mainland,[4] p. 56).

In 1963, he wrote about the possible demise of 'significance tests':

> In fact there are signs that mechanical 'significance' testing, although far from moribund, is not so vigorous as it was a few years ago; and with its death the problem of 'non significance' would no longer plague us. It is to be hoped that it would not be replaced by some other misunderstood mechanical trick.[31]

Mainland's optimism was misplaced. Fifty years later, the misuse and misinterpretation of significance tests is a bigger concern than ever.

Cluster randomisation

In his 1952 book[4] (p. 114), Mainland provided:

> ... what might be the first attempt in the medical literature to distinguish randomized trials by the unit of allocation. Indeed, in spite of some largely isolated examples, it was not until a brief but seminal article by Cornfield[34] that these ideas were brought to wide attention to researchers in the health sciences.[35]

Units of analysis

Mainland addressed a related issue, 'spurious replication', in his 1952 text (Mainland,[4] p. 32) and at rather

greater length in his second edition.[12] As noted by Bolton:

> Mainland gives other examples, but gets right to the point, defining the analysis of multiple observations from individual units (patients, for example) as mixed sampling. He contends that one has to be very careful about the objective of the experiment. Are we interested in a population of patients or in a population of readings from an individual patient?[36]

Comparing methods of measurement

Mainland criticised the use of the correlation coefficient for comparing methods of measuring a quantity:

> Akin to this misuse of r is the habit of employing it to express the reliability of a technique when an observer has made duplicate measurements or when two observers have measured the same thing. Even when the coefficient is 0.95 or higher, it does not tell us whether, for the purpose in hand, the differences between the duplicate readings are trivial or serious. (Mainland,[4] p. 334)

A little later, in 1955, he wrote:

> From the series of differences (reading by standard method minus reading by easier method) find the mean difference, i.e., the systematic difference between the two methods, and find the standard deviation of the series, i.e., the variable or random difference between the methods.[37]

This is essentially the approach recommended by Bland and Altman 30 years later.[38] In fact, Mainland had expressed similar ideas back in 1938.[39]

Surrogate measures

Mainland was among the first to draw attention to the issue of 'surrogate outcomes', as we now call them.[40] In his 1963 textbook, he asked 'Will the variables that we observe be the variables that we really wish to know about?'[12] He observed that 'if we are substituting something that is easy to observe for something that is difficult to observe, we have no right to do so unless we know the connection between the two things'. Mainland referred to the practice as the 'substitution game', attributing this term to Yerushalmy, and discussed the inferential challenges associated with such outcomes.

A few years later, he gave similar critical attention to composite indices of disease severity, which were common in studies of rheumatoid arthritis.[41]

Missing data

Mainland's 1963 textbook includes a whole chapter on 'Lost information', including discussion of both how to minimise losses and how to analyse data when there are missing observations, focusing in the latter on strategies rather than statistical procedures. He observes that the approach should be determined 'before our decision can be influenced by the outcome of the trial'. (Mainland,[12] p. 182)

Combining data from multiple studies

In his 1948 mini-text, Mainland considered the question of combining data from multiple similar studies.[9] He observed that simply collapsing the data as if from a single study 'entails a risk of fallacious conclusions from heterogeneous data'. Long before the term meta-analysis was introduced, Mainland used methods based on combining test statistics or *P* values, rather than effect estimates.

Reporting of research

Mainland was one of the first to recognise the critical importance of how research studies are reported.[28] Within the unusual closing chapter on publication in his 1938 textbook, he addressed tabular data, the importance of assessing the reliability of research findings and the importance of publishing 'negative evidence', and there were two pages addressing summaries and abstracts.[3]

Several of Mainland's Notes addressed deficiencies in publications. Note 10 of Notes on Biometry in Medical Research[21] discussed in detail the critical review of a published report of a clinical trial. It includes 10 lists of questions (56 items in all) for peer reviewers to consider.

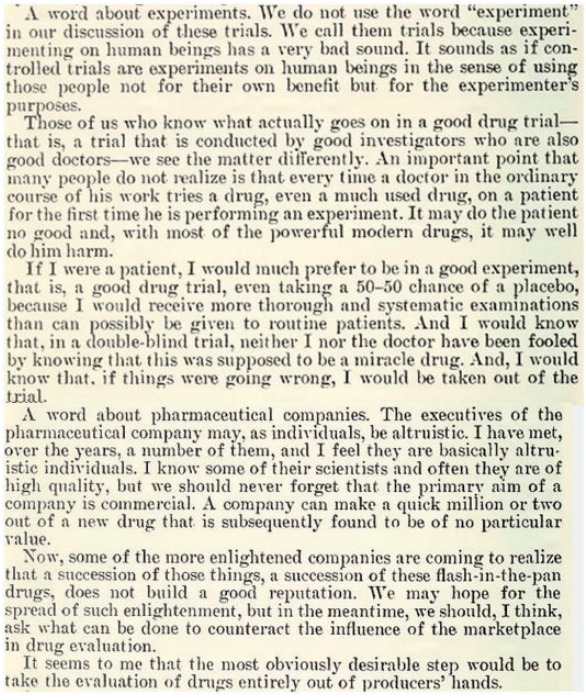
Clinical trials

As noted above, the opportunity to work on clinical trials was a major reason for his radical move from anatomy in Halifax to statistics and clinical trials in New York. In his last publication, he recalled that he had been 'enthralled by the earliest controlled therapeutic trials, which applied statistical thinking – realistic attention to the effects of variation and the risks of bias'.[30] Given his enthusiastic endorsement of Fisher's methods, and randomisation in particular, this move may perhaps not have been so surprising.

In New York, he worked full-time on multicentre therapeutic trials in rheumatology.[1] Within a few years, he had published an article about clinical trial methods[42] and more such articles followed.[19,43] Also, many of the statistics notes addressed issues arising in clinical trials. However, over more than 20 years, he was co-author of only a handful of publications of the results of trials, the first not until 1962[44] and the last in 1973.[45] This record presumably reflects the collaborative publication practices of the time, as it is clear from his publications and unpublished notes that he spent a lot of time working on the design and analysis of clinical trials.

Congressional hearings (1968)

In 1968, Donald Mainland was an expert witness in Congressional hearings on Competitive Problems in the Pharmaceutical Industry.[5] Early in his testimony, Mainland offered some general remarks about the value of good controlled trials (experiments):



A word about experiments. We do not use the word "experiment" in our discussion of these trials. We call them trials because experimenting on human beings has a very bad sound. It sounds as if controlled trials are experiments on human beings in the sense of using those people not for their own benefit but for the experimenter's purposes.

Those of us who know what actually goes on in a good drug trial—that is, a trial that is conducted by good investigators who are also good doctors—we see the matter differently. An important point that many people do not realize is that every time a doctor in the ordinary course of his work tries a drug, even a much used drug, on a patient for the first time he is performing an experiment. It may do the patient no good and, with most of the powerful modern drugs, it may well do him harm.

If I were a patient, I would much prefer to be in a good experiment, that is, a good drug trial, even taking a 50–50 chance of a placebo, because I would receive more thorough and systematic examinations than can possibly be given to routine patients. And I would know that, in a double-blind trial, neither I nor the doctor have been fooled by knowing that this was supposed to be a miracle drug. And, I would know that, if things were going wrong, I would be taken out of the trial.

A word about pharmaceutical companies. The executives of the pharmaceutical company may, as individuals, be altruistic. I have met, over the years, a number of them, and I feel they are basically altruistic individuals. I know some of their scientists and often they are of high quality, but we should never forget that the primary aim of a company is commercial. A company can make a quick million or two out of a new drug that is subsequently found to be of no particular value.

Now, some of the more enlightened companies are coming to realize that a succession of those things, a succession of these flash-in-the-pan drugs, does not build a good reputation. We may hope for the spread of such enlightenment, but in the meantime, we should, I think, ask what can be done to counteract the influence of the marketplace in drug evaluation.

It seems to me that the most obviously desirable step would be to take the evaluation of drugs entirely out of producers' hands.

Rodwin noted that 'the subcommittee heard testimony from several individuals proposing reforms that spanned a continuum from modest changes in current arrangements, to shifting the responsibility for testing drugs' safety and efficacy from drug firms to the federal government'.[46] He summarised Mainland's proposal as follows:

> Dr. Donald Mainland, who coordinated research for the American Rheumatism Association's Cooperating Clinics Committee, testified that it was current practice for the drug firm seeking marketing approval to act as an intermediary between the FDA staff and third-party testers. This arrangement allowed drug firms to influence the trials as well as the communication between testers and the FDA. Dr. Mainland suggested that Congress, 'take the evaluation of drugs entirely out of the producer's hands', after the completion of toxicological testing on animals, in order to remove the possibility of the producer biasing the process. Dr. Mainland proposed the creation of an independent, not-for-profit drug-testing agency that would provide grants for research in a manner roughly analogous to the NIH. He suggested that a council of experts from universities and research institutions should invite senior investigators to form 'working parties' for individual drugs. These 'working parties' would then choose teams of suitable investigators to conduct the safety and efficacy studies. The agency should be funded largely by the pharmaceutical industry in a manner that did not allow it to 'influence the disposal of the money or interfere in any way with the trials or the results'.

It seems likely that his proposal was heavily influenced by bad experiences in the clinical trials he had been involved in, but there are no accounts of such problems among the Notes he published around that time.[21]

After retirement

After Mainland retired from his post in New York University in the early 1970s, he and his wife Ruth moved to Kent, Connecticut. Thereafter, he published very little and seemingly had little academic activity.

His last publications included a 1982 paper 'Medical statistics – thinking vs. arithmetic', in which he revisited a theme he had long pursued,[26] and two personal views in the *BMJ* in 1984.[47] His last, posthumous publication was 'Some statistical thoughts on neurobehavioral testing', in which he addressed rank methods, multiple regression and composite indices.[30]

Donald Mainland died in July 1985. I have not found any obituary. Harry Marks, medical historian, found no evidence that any of Mainland's papers had been archived (personal communication, 2 February 2009).

Final words

The last of Mainland's Notes on Biometry in Medical Research was titled 'Envoi, with a vacillating hope'.[21]

Here he observed that:

> The Notes have been a continuation of the attempt, begun in the 'Notes from a Laboratory of Medical Statistics', to distinguish between the sense and the nonsense that statistical methods offer to medicine. In preparing the later notes, I have, I think, introduced more unsolved problems, questions without answers, than in earlier ones, in the hope that they will stimulate other research workers to continue the effort.

The closing sentences of this final Note reiterated an important idea from several earlier writings, and appear again in Mainland[26] – the need for medical statisticians to be embedded in real world research and not (too) mathematical:

> What disturbed me, even more, was the suggestion that theory was superior to application, because that is the attitude that will be met by research workers who are trying to think clearly about the subject. They will need the help of professional statisticians well-versed in theory; and all that I can say is: 'Try to get hold of someone who, like some of the professional statisticians mentioned in certain of the Notes, are close to thinking in real world research, and are willing to face frankly the defects of statisticians' efforts. Good luck in your search!' (Mainland,[21] p. 676)

Donald Mainland's career was remarkable, with a unique move from anatomy to medical statistics and clinical trials. His background in anatomy was fundamental in shaping his ideas about the place of statistics in clinical research. He exerted a considerable influence on those who came into contact with his writings, either published or privately circulated, or who were lucky enough to have his direct input to their projects.

As reported in the congressional hearings, Mainland had asked Stanley Schor, a medical statistician, to review his published report of a randomised trial.[44] Schor commented:

> It is, I think, the type of analysis that should be kept as a reference by every clinic investigator. Many times I am asked, are there any studies that have been published that you think are really good in terms of drug trials. Of course, every drug trial has its own bundle of problems, and it is not very useful to set up a step-by-step procedure which is to be used by all drugs in all cases. However, the analysis in this paper brings out so many important points which the usual clinical investigator is either not aware of or simply does not take into consideration that it should be required reading for all the people engaged in clinical trials. (U.S. Government,[5] p. 3348)

Donald Mainland could not have been as influential as he was had he not had both the ability to think clearly and also to write well. His writing was clear, he eschewed jargon, and he wrote really well for his target readership. His contributions should be remembered. His approach is one to emulate.

Donald Mainland in 1980 [Photo: Frederick P Glick]

Supplementary Appendix 1 presents selected observations made by Donald Mainland. Supplementary Appendix 2 presents some comments made about Donald Mainland. A list of the publications of Mainland is available here.

Declarations

Competing interests: None declared.

Funding: None declared.

Ethics approval: Not required.

Guarantor: DA.

Contributorship: Sole authorship.

Acknowledgements: I thank Ned Glick for helpful discussions and for making available the photographs of Donald Mainland taken by his father, Frederick P Glick. I thank David Colquhoun for helpful comments.

Provenance: Invited article from the James Lind Library.

References

1. Mainland D. Personal view. *BMJ* 1980; 280: 1269.
2. Mainland D. The rise of experimental statistics and the problems of a medical statistician. *Yale J Biol Med* 1954; 27: 1–10.
3. Mainland D. *The Treatment of Clinical and Laboratory Data: An Introduction to Statistical Ideas and Methods for Medical and Dental Workers*. Edinburgh: Oliver and Boyd, 1938.
4. Mainland D. *Elementary Medical Statistics: The Principles of Quantitative Medicine*. Philadelphia: WB Saunders Co, 1952.
5. U.S. Government. Competitive problems in the drug industry. Hearings before the Subcommittee on Monopoly of the Select Committee on Small Business. United States Senate Ninetieth Congress, first and second sessions. Present status of competition in the pharmaceutical industry. Part 7 Washington DC, 1968.
6. Mainland D. Statistical ward rounds – 16. *Clin Pharmacol Ther* 1969; 10: 576–586.
7. Chalmers I. Statistical theory was not the reason that randomization was used in the British Medical Research Council's clinical trial of streptomycin for pulmonary tuberculosis. In: Jorland G, Opinel A, Weisz G, eds. *Body Counts: Medical Quantification in Historical and Sociological Perspectives*. Canada: McGill-Queen's University Press, 2005: 304–334.
8. Mainland D. Statistics in clinical research: some general principles. *Ann NY Acad Sci* 1950; 52: 922–930.
9. Mainland D. Statistical methods in medical research. I. Qualitative statistics (enumeration data). *Can J Res* 1948; 26: 1–166.
10. Mainland D and Sutcliffe MI. Statistical methods in medical research. II. Sample sizes required in experiments involving all-or-none responses. *Can J Med Sci* 1953; 31: 406–416.
11. Mainland D. The planning of investigations. *Methods Med Res* 1954; 6: 138–145.
12. Mainland D. *Elementary Medical Statistics: The Principles of Quantitative Medicine*, 2nd edn. Philadelphia: WB Saunders Co, 1963.
13. Mainland D. Statistics in medical research (12 chapters, 3 co-authored by L Herrera) In: Steele JM, ed. *Methods in Medical Research*. Vol. 6. Chicago: Year Book Publishers Inc., 1954: 121–214.
14. Mainland D. Use of case records in the study of therapy and other features in chronic disease. I. Planning the survey. *Ann Rheum Dis* 1955; 14: 337–352.
15. Mainland D. Notes on the planning and evaluation of research, with examples from cardiovascular investigations. I. *Am Heart J* 1958; 55: 644–655.
16. Mainland D. Notes on the planning and evaluation of research, with examples from cardiovascular investigations. II. *Am Heart J* 1958; 55: 824–837.
17. Mainland D. Notes on the planning and evaluation of research, with examples from cardiovascular investigations. III. *Am Heart J* 1958; 55: 838–850.
18. Mainland D. The use and misuse of statistics in medical publications. *Clin Pharmacol Ther* 1960; 1: 411–422.
19. Mainland D. The clinical trial – some difficulties and suggestions. *J Chronic Dis* 1960; 11: 484–496.
20. Mainland D. Statistical ward rounds – 1. *Clin Pharmacol Ther* 1967; 8: 139–146.
21. Mainland D. Notes on biometry in medical research. (Edited by MC Miller III) [104 items in 13 Monographs, 1967 to 1970, published by Veterans Administration, Washington DC]. Ann Arbor, MI: Biometry Imprint Series Press, 1978. (Distributed by University Microfilms International).
22. Mainland D. Notes from a laboratory of medical statistics. Volumes I and II. (Edited by MC Miller III) [A series of 145 mimeographed notes distributed by the author (1959 to 1966)]. Ann Arbor, MI: Biometry Imprint Series Press, 1979. (Distributed by University Microfilms International).
23. Mainland D. Statistical ward rounds. (Edited by MC Miller III) [18 articles reprinted from *Clin Pharmacol Ther* 1967 to 1969]. Ann Arbor, MI: Biometry Imprint Series Press, 1979. (Distributed by University Microfilms International).
24. Feinstein AR. Clinical biostatistics. 1. A new name – and some other changes of guard. *Clin Pharmacol Ther* 1970; 11: 135–148.
25. Lassere M. Are reporting standards of diagnostic test evaluation unrealistic? *J Rheumatol* 2010; 37: 220–222.
26. Mainland D. Medical statistics – thinking vs arithmetic. *J Chronic Dis* 1982; 35: 413–417.
27. Mainland D. Problems of chance in clinical work. *Br Med J* 1936; 2: 221–224.
28. Altman DG and Simera I. *A History of the Evolution of Guidelines for Reporting Medical Research: The Long Road to the EQUATOR Network*. JLL Bulletin: Commentaries on the history of treatment evaluation. See www.jameslindlibrary.org/articles/a-history-of-the-evolution-of-guidelines-for-reporting-medical-research-the-long-road-to-the-equator-network/ (2015, last checked 4 December 2019).
29. Schor S and Karten I. Statistical evaluation of medical journal manuscripts. *JAMA* 1966; 195: 1123–1128.
30. Mainland D. Some statistical thoughts on neurobehavioral testing. *Obstetric Anesthesia Digest* 1985; 5: 90–94.
31. Mainland D. The significance of "nonsignificance". *Clin Pharmacol Ther* 1963; 4: 580–586.
32. Mainland D. Is the difference statistically significant? An innocent request for quack treatment. *Clin Pharmacol Ther* 1969; 10: 436–438.
33. Neyman J. Outline of a theory of statistical estimation based on the classical theory of probability. *Philos Trans R Soc Lond A* 1937; 236: 333–380.
34. Cornfield J. Randomization by group: a formal analysis. *Am J Epidemiol* 1978; 108: 100–102.

35. Klar N and Donner A. *The Impact of E.F. Lindquist's text "Statistical Analysis in Educational Research" on Cluster Randomisation*. JLL Bulletin: Commentaries on the history of treatment evaluation. See www.jameslindlibrary.org/articles/the-impact-of-ef-lindquists-1940-text-statistical-analysis-in-educational-research-on-cluster-randomization/ (2004, last checked 4 December 2019).
36. Bolton S. Independence and statistical inference in clinical trial designs: a tutorial review. *J Clin Pharmacol* 1998; 38: 408–412.
37. Mainland D. An experimental statistician looks at anthropometry. *Ann NY Acad Sci* 1955; 63: 474–483.
38. Bland JM and Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307–310.
39. Mainland D and Stewart CB. A comparison of percussion and radiography in locating the heart and superior mediastinal vessels. *Am Heart J* 1938; 15: 515–527.
40. Lassere MN. The Biomarker-Surrogacy Evaluation Schema: a review of the biomarker-surrogate literature and a proposal for a criterion-based, quantitative, multidimensional hierarchical levels of evidence schema for evaluating the status of biomarkers as surrogate endpoints. *Stat Meth Med Res* 2008; 17: 303–340.
41. Mainland D. The estimation of inflammatory activity in rheumatoid arthritis. Role of composite indices. *Arthritis Rheum* 1967; 10: 71–77.
42. Mainland D. The modern method of clinical trial. In: Steele JM (ed.) *Methods in Medical Research*. Vol 6, Chicago: Year Book Inc, 1954, pp.152–158.
43. Mainland D. Experiences in the development of multiclinic trials. *J New Drugs* 1961; 1: 197–205.
44. Mainland D and Sutcliffe MI. Hydroxychloroquine sulphate in rheumatoid arthritis, a six-month, double-blind trial. *Bull Rheum Dis* 1962; 13: 287–290.
45. Mainland D, Sutcliffe MI and O'Brien WM. A controlled trial of gold salt therapy in rheumatoid arthritis. *Arthritis Rheum* 1973; 16: 353–358.
46. Rodwin MA. Independent clinical trials to test drugs: the neglected reform. *Saint Louis Univ J Health Law Policy* 2012; 6: 113–166.
47. Mainland D. Statistical ritual in clinical journals: is there a cure? *BMJ* 1984; 288: 841–843 (Part I) and 920–922 (Part II).
48. Mainland D. A study of the sizes of nuclei in ovarian stroma. *Anat Rec* 1931; 48: 323–40.
49. Mainland D. Chance and the blood count. *Can Med Assoc J* 1934; 30: 656–658.