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26th August, 1993.

Dr Hugh Fraser,
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Dear Dr Fraser,

Thankyou for your letter of 20th August, and the enclosed papers. You ask for more information regarding my request for data, so the following is a rather more detailed outline of what type of data I am looking for, and why; the 'why' being first.

As I mentioned in my first letter, originally we started this work with the intention of refining our BSE predictions. In order to predict numbers of cases in the future, one necessary piece of information was the possible range of incubation periods, and the proportion of cases occurring at each time point throughout that range - i.e. the frequency distribution (*f/d*) or 'shape', of the incubation period (*i/p*) range. Due to the phenomena of left and right censoring, it is very difficult (virtually impossible) to obtain that information accurately during the course of an epidemic, and particularly so during the early stages, when the longest possible *i/ps* will not yet have occurred. We therefore decided to re-examine our early estimates of this *i/p f/d*, which were based on Sartwell's hypothesis that generally the *i/p f/d* of infectious diseases followed a 'log-normal' curve. Sartwell, however, working in the early 1950's, had not looked at TSE's, or other diseases with a long *i/p* often measured in years; perhaps there are differences. There were a number of possible approaches to this problem, and these were followed up, including examination of the *i/p* (or age at onset where necessary) *f/d* of non-epidemic TSEs thus avoiding the left and right censoring problems.

I have been given access to considerable raw data on human TSE's, from which it has become apparent that the 'age at onset' *f/d* for CJD (and possibly GSS) does not necessarily follow a log-normal curve, even when split into identified subsets (e.g. familial CJD, sporadic CJD). There are a number of possible reasons for this; however, it is relevant that other workers have examined some genetically inherited diseases, resulting in the suggestion that they do have a log-normal age at onset distribution (at least for some diseases). 'Age at onset' is therefore likely to be a reflection of particular aetiological factors, about which, for sporadic CJD at least, much is yet unknown. It has therefore been suggested that examination of the *f/d i/p* of other groups with TSE's, and comparison with that of CJD subsets might help to elucidate aetiological mechanisms for sporadic CJD in particular; i.e. almost a reversal of the original undertaking.

What I need to do now, therefore, is to construct a 'baseline'; that is to examine certain groups of animals with known *i/ps* (most likely therefore to be experimental animals), to look at the *i/p f/d*, to see if under known sets of controlled conditions, with a known infection mechanism (e.g. parenteral introduction of infectious material at a similar site, and of a similar dosage) a repeatable, stable shape for the *i/p f/d* (e.g. perhaps log-normal) is demonstrable; the actual mean values of the *i/p* ranges are not the important factor here. Since most published papers give only the mean & SD, and I need each individual animals *i/p* to construct & examine the shape of the *f/d*, I am having to ask experimenters for the raw *i/p* data for each animal in appropriate, identified sets.

Briefly, what I hope to be able to find are several sets each of several hundred small laboratory animals (e.g. mice, hamsters), each of the sets being different in some significant way (e.g. dif-

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ferent species entirely, or different strain of mouse, etc.) , and animals within each set being as similar as possible wrt dose, infection method, age at infection, agent derivation, etc, (though it may not be possible to find 'identical' sets), for as many TSE's as possible, and to obtain individual incubation periods for each animal within the set, plus the other necessary information on the set. With respect to large animals, ideally I would like something similar, but I doubt if it is possible to find sets of hundreds of sheep or goats; I shall probably have to manage with something much smaller. I have set up a rather complex database to receive this information, and hope at least to get sets of experimental scrapie, BSE and CJD data. I am therefore contacting those people who might be able to help with this, as well as looking through published work for any large sets where individual i/p is given (some do, but often in a small graph, which needs very good eyesight to decipher).

I hope this answers your questions about why I am asking for this data, and goes a little way towards explaining more fully what I need. Once again, thanks for taking an interest thus far, and I will ring you about it shortly, to see if you need any further information before approaching your colleagues.

Yours sincerely,

A handwritten signature in black ink, appearing to be 'M. Wooldridge', written in a cursive style.

Marion Wooldridge
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(Ext: 2621).