Ethical Considerations Involved in Trace Element Research with Humans

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Keywords ethics, human volunteers, radioisotopes

Research in nutrition and metabolism, like all areas of biomedical research, must ultimately involve experimentation with human subjects. Despite their many metabolic and physiological similarities, rats are not just little humans. The public's interest in regulating biomedical research has been strong since World War II, and continues to increase. Revelations concerning use of radioactive materials in unknowing or poorly informed subjects in the United States during the 1940's, 50's, and 60's (Mann 1994) resulted in a massive nationwide investigation that was covered not just by scientific publications, but by mass media across the country. Even popular magazines have recently carried articles advising readers of what to consider before volunteering as research subjects.

Nutrition research in humans must be carried out in accordance with international principles governing all biomedical research, such as the Nuremburg Code (Anon. 1949) and the Declaration of Helsinki (World Med. Assoc. 1964 et. seq). In addition, most nations have their own, more detailed legislation and regulations governing such work, and individual institutions further regulate the conduct of such investigations. Since a large proportion of research on trace element nutrition and metabolism is done with healthy subjects, these moral and legal codes place severe constraints on what is allowable. Research with healthy subjects cannot be legitimately carried out unless the importance of the objective is in proportion to the inherent risk to the subject, and concern for the subject must prevail over the investigator's desire for knowledge. This discussion will be limited to research with healthy humans, where the main benefit to the subject is the good feeling that comes with participation in accruing knowledge that will benefit a large number of people.

Several conditions raise general ethical concerns regarding research in healthy subjects: pregnant and lactating women; infants and children; fertile women; minors who cannot give legal consent; prisoners; adults incapable of giving informed consent. Recently, fertile men have also been added to this list. Ethical/moral issues may also arise in the context of religious objections to certain experimental procedures.

For trace element research, manipulation of dietary intakes must be within "normal" ranges of dietary intake of an element when pregnant or lactating women and infants are involved, because both deficiency and excess of many trace elements may be teratogenic, toxic, or interfere with normal growth and development. Fertile women involved in studies where dietary intakes are substantially greater or less than normal must be well informed of the potential risks of pregnancy during the study. Trace element intake continues to affect both physical and cognitive development after infancy (often irreversibly), so the constraints on dietary or other intake of trace elements that apply to pregnancy, lactation, and infancy apply to children as well.

Researchers have tended not to consider potential effects on male fertility. There is emerging appreciation that not all effects on male fertility are rapidly reversible. Hawkes (personal communication 1996) reported effects of Se intake on sperm counts and motility. Four weeks of dietary Se intake lower than average (13 μg/d) resulted in increased sperm motility and greater semen volume, while dietary Se greater than normal (356 μg/d) resulted in decreases in sperm motility. The effects were not reversed during the study, so it is not known how long they last. Thus, in some cases, it will be necessary to advise male subjects of potential negative effects on future fertility.

Two other situations that have come to the author’s attention have not been much written about. The first is religious objections to experimental procedures that are not otherwise unethical. A study of Zn metabolism in young men involved collection of semen samples; members of the nursing staff objected because it involved masturbation by the subjects. The investigators obtained approval of the experimental protocol from a Roman Catholic priest. Care was taken to ensure that information for prospective volunteers was clear about the inclusion of this activity as part of the study. Staff members who objected to being involved were scheduled so as not to have to transport samples.

Another scenario that has emerged in a new guise is the possibility of completely unqualified persons carrying out research with humans, without any review of experimental procedures. The author became aware of this through a telephone call from a high school student who was planning to do a science fair project involving supplementation with Se tablets purchased at a local store. The student was unaware of any necessity for review of her experimental plans, for involvement of a medical professional, for obtaining informed consent from subjects, or any other constraints. Many of her anticipated subjects were minors. Her teacher was also unaware of these requirements.

Although there are many difficulties associated with the use of radioisotopes in healthy humans, there are some conditions under which it can be both practical and ethical. For certain trace elements, (e.g., Cu, Zn, Fe, Mn) there are radioisotopes available with suitable half-lives and gamma energies such that experiments can be done in adults. Care must be taken to ensure that female subjects are not pregnant and are using contraception. Radiation exposures similar in magnitude to those encountered in various common activities, such as jet air travel or camping in the mountains, can be justified in subjects who derive no personal benefit from the procedure.

Finally, the issue of publication of experimental results must be considered. All of the usual ethical considerations relating to authorship, etc. apply to studies with humans. I propose an additional one: It is unethical to fail to publish publishable data obtained from research with subjects who derive no personal benefit from participation in the experiment. The reasoning for this is that in order to carry out these studies, one must justify the risks to the subjects largely on the basis of the benefit that the study will be for humanity. If the results of the study are sound, but are not published because of procrastination, laziness, or other fault of the investigator, this constitutes unethical conduct because no one can benefit from unpublished information.

References


Workshop Discussion

Following presentations by Peter Flanagan (The University of Western Ontario, London, ON, Canada) on ethical use of animals (Abstract 136. Ethical use of animals for experimentation and teaching) and by Phyllis Johnson (USDA, Albany, CA, USA) on ethical use of humans (Abstract 137. Ethical considerations involved in trace element research with humans), a lively discussion ensued.

There was some discussion about obtaining informed consent from subjects such as terminally ill patients (Solo Kuvibidilla, Louisiana State University, New Orleans, LA, USA) and in third world countries where literacy is a problem (Harold Sandstead, University of Texas Medical Branch, Galveston, TX, USA). Kenneth Wing (Umea University, Umea, Sweden) wondered how you can possibly get informed consent with a one-page consent form. There was also some discussion regarding the increasing length of consent forms being used.

A number of investigators discussed the ethics of treating or not treating control groups. Rosalind Gibson (University of Otago, Dunedin, New Zealand) had earlier commented on the difficulty of not treating control groups in a third world situation where four villages are involved in a dietary intervention study. All the children in the villages will be dewormed initially and, after the intervention period with two of the villages, the other two will be offered the same
treatment as the intervention villages. John Howell (Murdoch University, Murdoch, Western Australia) thinks that it is appropriate to treat control if positive results are obtained.

Harold Sandstead (University of Texas Medical Branch, Galveston, TX, USA) expressed some concerns about this approach as it may be difficult to actually do the follow-up treatment with the control groups. Kenneth Wing (Umea University, Umea, Sweden) suggested that problems such as these could be overcome at the design stage by using, for example, a cross-over design in the aforementioned example.

Richard Black (Kellogg Canada Inc., Etobicoke, ON, Canada) commented on the manner in which control groups are treated. For example, in a colon cancer trial where fat is being lowered and fibre increased, the control group will eat as usual even though the researchers feel that a high fat diet with low fibre affects the risk of CVD. Is it ethical then not to treat the control group? Les Klevay (USDA, Grand Forks, ND, USA) made a comment that we don’t indeed know that decreasing fat in the diet will decrease the risk of CHD.

Following the discussion on control groups, a discussion of ethics committees ensued. Gerry Combs (Cornell University, Ithaca, NY, USA) asked if anyone has evaluated decisions taken by investigational research boards (IRB’s) and whether there are differences among various IRB’s within countries, etc. Peter Flanagan (The University of Western Ontario, London, ON, Canada) said that IRB’s play a large role in Canada and the USA. Phyllis Johnson (USDA, Albany, CA, USA) pointed out that local standards are supposed to apply and that there would therefore be variability. When working with government agencies, such as the USDA, you need to go through the process more than once and one often gets different responses from each committee, thus enforcing the point of variability within a country, etc.

Judy Butler (Oregon State University, Corvallis, OR, USA) commented that a number of researchers work in a number of communities and need approval in each location. How much in the way of local standards can be imposed in another country?

Richard Black (Kellogg Canada Inc., Etobicoke, ON, Canada) commented that it seems that one can argue one’s case before an ethics committee and thus get approval which may or may not be based on merit.

Wanda Chenoweth (Michigan State University, East Lansing, MI, USA) commented that if a proposal can’t get past 20 people then it likely should not be done. The fine points will likely change with the composition of the committee.

Barbara Golden (University of Aberdeen, Scotland) suggested that researchers take care of their own personal moral and ethics codes and consider whether or not you or your children would undergo the intervention in a study.

John Howell (Murdoch University, Murdoch, Western Australia) pointed out that in Australia, ethics committees have been of benefit and believes that they have improved experimentation.

Gillian Lockitch (Vancouver, BC, Canada) noted that she has had trouble obtaining ethics approval for research to obtain normal values for laboratory measurements, but on the other hand, is it then ethical to do lab tests on others when there are no reference data with which to compare results?

Peter Flanagan (The University of Western Ontario, London, ON, Canada) asked about when is enough? How do you ever know. Is the quest for knowledge the driving force or are we keeping labs going by doing research?

John Sorenson (University of Arkansas, Little Rock, AR, USA) had comments to make about a few points. He feels that animal care committees are not necessary and that researchers should take it upon themselves to decide what research should be done. He doesn’t feel that one needs ethics approval for research with animals raised specifically for research. There should be no interference with the investigator’s plan. There was considerable disagreement with this point of view.

Joseph Prohaska (University of Minnesota, Duluth, MN, USA) says that he is in favour of academic freedom but there should be a critical review of the scientific procedure. The public needs to be served and we have to be aware of ethics and cost effectiveness.

John Sorenson (University of Arkansas, Little Rock, AR, USA) said that discoveries are made when there free intellectual pursuit and that progress will be restricted if we restrict research by stringent ethics committees.

Phyllis Johnson (USDA, Albany, CA, USA) commented that in some cases, as in government, research work is driven by the mission of the government.

Koen Wienck (University Hospital Utrecht, The Netherlands) added that responsibility should be added to the 3 R’s of research which Peter Flanagan mentioned in his talk.

Gerry Combs (Cornell University, Ithaca, NY, USA) closed the discussion by saying that responsibility really is the issue and that freedom does not come without responsibility. Further, increasingly institutional liabilities are guiding ethics committees.