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GUEST EDITORIAL

Ethical Problems in Research

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Medical research is expanding. Changes in Canadian patent laws have encouraged pharmaceutical companies to fund more research in this country. At Dalhousie University, clinical and basic science departments have become increasingly involved in clinical research, partly as a result of improved funding. Physicians are also carrying out more research in their offices, outside of the University setting. Ethical problems in medical research have always been important, but never before have these issues touched so many people. In September, 1989, the Department of Medicine at Dalhousie University held a symposium entitled "Ethical Problems in Research", to address some of these issues. Each speaker submitted a written manuscript and the Proceedings are included in this issue of the *Journal.*

The first speaker, Dr. Howard Morgan, is Director of Research at the Geisinger Clinic in Danville, Pennsylvania. He is a highly respected cardiologist, who chaired the National Institutes of Health Special Panel to Review Alleged Misconduct at Brigham and Women's Hospital/Harvard Medical School. The Panel was asked not only to review the fabrication of data by a physician, but also to address the adequacy of the hospital's and Harvard University's response, when the misconduct was reported. While this particular incident received much press coverge, partly because of where it took place, the pressures to publish research occur in all universities. Scientific misconduct not only involves such serious problems as the creation of fraudulant data but also includes seemingly minor transgressions, such as omitting certain experiments or patients, because they do not conform to the investigator's hypothesis. Merely by placing pressure on researh assistants, an investigator can unwittingly create an environment conducive to scientific misconduct. Dr. Morgan discusses these issues as he addresses the problem of what institutions can do to maintain scientific integrity.

Dr. Anitra Laycock is the chair of the Camp Hill Medical Centre Ethics Committee, which reviews ethical problems relating to patient care, and is a member of the Camp Hill Medical Centre Research Committee, which reviews ethical aspects of human research protocols. Beginning with a historical perspective, Dr. Laycock addresses the issue of informed consent. What constitutes adequate informed consent? Where do we fall short when we inform patients about our plans for them (whether or not they are research subjects)? What barriers exist to obtaining *informed* consent? Dr. Laycock's article

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is sobering as it recounts past transgressions by researchers and encouraging as it clearly outlines the basics necessary for adequately informing patients.

Dr. Abbyann Lynch is Director of the Westminister Institute for Ethics and Human Values in London, Ontario. Her article, "Placebo-controlled Trials in Terminally Ill Patients: What Place Compassion?", addresses a major problem arising in terminally-ill AIDS and cancer patients. When a new and untested medicine becomes available to treat and possibly cure patients with an "incurable" disease, what right does the medical community have to withhold the medication until adequate clinical trials are completed? How does one balance the desire to do no harm with a patient's desperation to try anything that might prolong life or cure a fatal disease? This dilema and public pressure has persuaded the Health Protection Branch in Canada and the Food and Drug Administration in the United States to develop a "fast track" for new drugs for terminally-ill patients. Some of the hazards of this approach, including increased morbidity and mortality, are already occurring in the United States. The traditional approach of doing a prospective, placebo-controlled trial, however, means delaying the widespread use of new drugs for months or even years.

Parkinson's disease is a slowly progressive, debilitating and, until recently, incurable disease. While the human data are preliminary, there is evidence that the transplantation of fetal adrenal tissue into the basal ganglia of the brain of at least some Parkinson's patients may reverse the manifestations of this disorder. Dr. Alan Fine and Dr. Nuala Kenny discuss the issues of fetal tissue transplantation from different perspectives. Dr. Fine is Associate Professor of Physiology at Dalhousie University. He is one of the principal investigators of a proposed research project to treat seriously ill Parkinson's patients with fetal adrenal transplantation. In his article he discusses the rationale and evidence supporting the use of fetal tissue to treat Parkinson's disease. He also addresses the ethical issues and the hurdles involved in obtaining ethical approval for such a trial. Sister Nuala Kenny is Professor and Head of the Department of Pediatrics at Dalhousie University. Dr. Kenny discusses the ethics of fetal tissue transplantation in its larger context, that of a society divided over the morality of abortion and the status and rights of the fetus. She argues that we cannot separate research involving human fetuses from the question of how the tissue itself was obtained.

The articles concerning research ethics in this issue of the *Journal* are meant to stimulate debate and heighten awareness of some difficult problems in clinical investigation. While the authors propose some answers to these problems, I believe these discussions best serve to define the ongoing debate about how we, as physicians, should conduct high quality and ethically sound medical research.

Finally, I wish to thank the Pharmaceutical Manufacturers Association of Canada for financial support of the Symposium and Laurie Quinn for her excellent secretarial assistance. □

EDITOR'S NOTE

The following are transcripts of papers presented at a symposium on Ethical Problems In Research, sponsored by the Department of Medicine, Dalhousie University, Halifax, N.S. on September 12, 1989.

Call for Nominations: Society Officers
The Medical Society of Nova Scotia

An election for the following positions will be held at The Society's Annual Meeting, November 15-17, 1990:

President-Elect

Chairman, Executive Council
(Currently G.A. Ferrier, eligible for reappointment.)

Vice Chairman, Executive
(Currently, Debora Ryan-Sheridan, ineligible for reappointment.)

Treasurer
(Currently, R.B. Auld, ineligible for reappointment.)

Honorary Secretary
(Currently, Shelagh Leahey, eligible for reappointment as Honorary Secretary.)

Nominations must be made to the Nominating Committee which consists of the Past Presidents of the Branches of The Society. The Nominating Committee must report its recommendations at least four weeks prior to the Annual Meeting. Nominations should therefore be put before them by the end of September at the latest. Nominations may also be made from the floor provided such nominations are placed in writing in the hands of the Executive Director not less than one week prior to the Annual Meeting. Such nominations must be signed by ten members of The Society in good standing and such nominations must be accompanied by the written consent of the nominee to serve, together with his/her Curriculum Vitae.

What Institutions Can Do To Prevent Scientific Misconduct

Howard Morgan,* MD

Danville, Pennsylvania

The spectrum of groups involved in the responsible conduct of research involves the investigator, institution, funding agency, congress and the press. None of these entities are behaving optimally to achieve the best environment for the responsible conduct of research.

The investigator is primarily responsible for defining the research and training practices within his/her laboratory. Willingness of the investigator to be accountable for all activities with the laboratory or research program is the bedrock upon which all other practices and procedures are built.

The institution can aid the investigator by defining its expectations for research and training practices including mentoring, data retention and authorship. The institution can also state clearly its criteria for professional accomplishment and put in place a well thought out set of procedures for investigating scientific misconduct when it is alleged. In this discussion, I will focus on the investigator's and institution's role.

Institutional oversight involves an equation with two major parties:

1) individual investigators; and
2) the institutional system in which the investigators work.

Individual investigators are responsible not only for their own conduct, but that of their trainees as well. They must be free to pursue new ideas and leads and to provide imaginative training unrestrained by restrictive institutional regulations. The *institutional system* provides the interface between those who conduct research and the general scientific community and the public-at-large. Institutions must be accountable to those that fund research to assure that it is conducted in a responsible manner and that monies are spent prudently within the guidelines of the granting agency. Institutional standards must be clear even if discomfort is produced for both parties to the equation.

ISSUES OF COMMON CONCERN TO INVESTIGATORS AND INSTITUTIONS

Individual investigators and the institutions in which they work face a number of common issues in the responsible conduct of research. These issues include:

1) expectations for training and mentoring;
2) standards for handling, storage and maintenance of data;
3) the meaning and responsibilities of authorship of a scientific paper; and
4) the definition of scientific accomplishment.

Individual investigators must set their own standards in dealing with each of these issues. These standards, however, must be consistent with institutional guidelines that allow the insitution to meet its broad responsibilities to science and the public. Responses to these issues must serve the goal of conducting the best science and scientific training in a supportive and collegial atmosphere. The standards and practices of individual investigators are legitimate concerns of institutions. Similarily, institutional guidelines may either enhance or impede the productivity of individual investigators.

In many institutions, the issues listed above have not been discussed openly and institutional guidelines have not been developed. In fact, the Harvard guidelines that appeared in the spring are among the first. Where guidelines do exist, a system to assure that individual investigators comply has not been worked out or is inadequate and ineffective. Neither individual investigators nor institutions should apologize for their interests and concerns for the activities of each other. Open constructive interchange is the key. Continued lack of dialogue dealing with the responsible conduct of research based on claims of academic freedom by investigators and ultimate authority by institutions will result in the entry of third parties, such as the federal government, into our initial equation that involved only two parties. Government regulatory action may not be the best solution for either individual investigators or institutions.

In seeking to promote scientific responsibility and quality assurance in health sciences research, what principles should apply in developing an individual and institutional response to the issues of training, data handling and management, authorship and measures of scientific success?

Expectations for Training and Mentoring

In regard to training, three parties are already involved, the trainee, mentor and institution. The goal of interactions among these parties is the establishment of a collegial atmosphere in which all members of the research unit can contribute to its scientific program and members of the group can receive informal peer review.

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From the point of view of institutional oversight, two components of the training program deserve attention. First, the institution needs to know that each trainee is receiving effective supervision. If the senior investigator in the laboratory is not able to provide oversight in the design and conduct of experiements, another experienced investigator within the laboratory should be assigned this responsibility. The trainee should be informed who is his or her mentor. Secondly, the institution must be assured that each new trainee is provided with applicable institutional and governmental rules for conduct of studies that involve human subjects, animals, radioactive or hazardous substances and recombinant DNA. The relevant regulations must be discussed in detail with each new investigator and each investigator needs to demonstrate some understanding of these regulations.

Standards for Handling, Storage and Maintenance of Data

Historically, the institution has delegated its oversight responsibilities in this area to individual investigators. In the large majority of cases, data have been handled in an appropriate and responsible manner. However, investigations of a number of cases of alleged scientific misconduct have revealed the absence of a complete set of verifiable data. Without access to the primary data, errors cannot be distinguished from scientific misconduct. Therefore, protection of both the individual investigator and institution requires institutional oversight that includes monitoring of methods for data handling, storage and maintenance.

The distinction between error and fraud must be clear to all. *Error* is part of science. If sufficient information were avialable to know precisely what should be done, the activity would not qualify as research. Error is particularly prevalent in the interpretation of data where incomplete knowledge make alternative explanations possible. Error is not deserving of criticism so long as it is clearly acknowledged.

Several principles pertain to data handling so that error can be clearly distinguished from *fraud.* First, primary laboratory data must remain in the possession of the unit that collected it. The institution must have "for cause" access to data. Secondly, trainees may copy data books and other forms of primary data but the original material must remain in the laboratory at all times and optimally be retained for the life of the unit. Move of laboratory from institution must include arrangement for data maintenance. Thirdly, the storage and maintenance system must be adopted to the forms of primary data that are collected. For example, original protein or nucleic acid gels, DNA sequencing gels and electron micrographs can not be stored in bound laboratory notebooks. Each laboratory unit should be required to develop an effective data handling, storage and maintenance system and to report the components of the system to the institution. At least annually, an institutional official should inspect operation of the system and evaluate its effectiveness by the investigators ability to retrieve a verifiable data set from representative experiments. In short, the data maintenance system must be known to work. The presence of a set of verifiable data is the sure way to distinguish error from fraud. On the other hand, random audits by governmental bodies will stifle the atmosphere of free inquiry and creative science.

Authorship of Scientific Papers and Publication Practices

Institutional oversight regarding authorship and publication is focussed on three facets of the topic. First, the institution must be assured that each coauthor has made a significant intellectual or practical contribution to the work. One means of assuring this practice is to require that the final draft of the manuscript be submitted to the journal and to the departmental chair or other institutional official with a signed statement defining each authors contribution, indicating that each coauthor has reviewed and approved the manuscript to the extent of their contribution and expertise, stating that no other persons qualify as an author, and certifying that the primary data on which the paper is based are present in the laboratory. One of the authors should accept responsibility for the entire manuscript. Secondly, the institution may request the author responsible for the entire paper to go over the primary data that are summarized in the manuscript with the departmental chair, when review of the manuscript raises questions regarding reproducibility or validity of research findings. Thirdly, departmental chairs or other institution officials should monitor the publciation practices of individual scientists to detect irregularities such as publication of portions of a study, submission of multiple papers or abstracts with essentially the same content and rapid publications with insufficient documentation of reproducibility or significance.

Institutional oversight is not intended to replace the peer review system of scientific journals which assesses the merit and significance of scientific findings with the aid of highly qualified experts who do not have a conflict of interest engendered by the same institutional affiliation. Thus, the institutional review process should not attempt to duplicate journal peer review but should be designed to guarantee that laboratory records exist and that the research practices conform with professional standards.

Definition of Scientific Accomplishments

In the past four decades, progressively greater emphasis has been placed on the number of publications produced by an individual investigator in addition to the quality of the work that is reported. Clearly, it is easier to count the numbers of papers in peer-reviewed journals, of symposia papers and of abstracts than it is to critically assess the publications uniqueness of approach

and contribution to new knowledge. Both the institutions and granting agencies are to blame for the increasing emphasis on quantity over quality of publication.

Recenlty, Harvard Medical School took a new approach by limiting the number of publications to be reviewed at times of staff appointment or promotion. The intention is to encourage and reward bibliographies containing fewer and more substantive publications rather than many fragmented and redundant reports. For example, no more than five papers are reviewed for appointment as an Assistant Professor and nor more than ten papers for appointment or promotion to Professor. This change in focus should be emulated by other institutions and may have far-reaching consequences for the responsible conduct of research in the US and elsewhere. The goal is to encourage papers that report complete studies that make a lasting contribution.

In summarizing institutional oversight, issues of common concern have been identified. If these issues are discussed in an open and positive manner, research can be conduted in a more responsible manner in the health sciences.

RESEARCH SPONSOR GUIDELINES AND REGULATIONS

These guidelines have a strong effect on the research environment of the instituion. Research sponsors require a detailed scientific proposal, a budget, and assurances that the institution will comply with relevant governmental regulations regarding human subjects, animals, radioactive and hazardous materials and recombinant DNA. Fiscal management of monies that are awarded must be accomplished in a thoughtful and prudent manner by the institution, within the grant management policies of the agency.

The major way in which research sponsors strongly influence the responsible conduct of research is in evaluation of the scientific accomplishments by individual investigators and the impact of these evaluations on the priority scores and likelihood of funding. As indicated earlier, the peer review process appears to have placed more emphasis on numbers of publications in peer-reviewed journals than the new knowledge that has been gained. To a large extent, publications in the most prestigious journals of the field are taken to be of equal scientific value, even though one paper may put forward an important new concept and the other is largely archival. As for faculty or staff appointments and promtions, evaluation of scientific accomplishment on a given project during the past three years should be based on the evaluation of a limited number of publications. If the major emphasis were placed on the quality of the work, peer-review would be more meaningful, fewer and more significant publications would result, and science would be conducted in a more responsible fashion. It may be desirable to develop peer review guidelines for each major research sponsor to assure that reviewers understand the criteria that should guide their evaluation, decisions and recommendations.

INSTITUTIONAL OVERSIGHT OF ALLEGATIONS OF SCIENTIFIC MISCONDUCT

Finally, procedures must be in place for investigation of allegations of scientific misconduct. Guidelines have been developed by a number of universities for an institutional response to allegations of scientific misconduct. If these guidelines are followed, the rights and reputations of all parties will be protected including the individual who reported misconduct in good faith. If an initial review determines that there is sufficient basis to pursue the allegations, a committee should be appointed to conduct a prompt and thorough investigation of the alleged misconduct. Consideration should be given to the review of all research with which the individual is involved. Granting agencies that sponsored the work should be notified.

Recent events reaching the public press highlight the key role of the institution in conducting a thorough investigation by persons not connected with the accused through personal or professional ties. A thorough investigation will exonerate those falsely accused and will protect the institution, co-workers, granting agencies and the public from those guilty of scientific misconduct in any of its forms. When reports of misconduct are not thoroughly explored, the accused as well as those making the allegation remain vulnerable to hostile acts by co-workers, the institution, news media and government officials. Presumptions of innocence of well-known and respected scientists that leads institutions to conduct a superficial investigation is a terrible disservice to all. Because scientists are held to a higher standard than the general public as the result of the nature of their work and its support with public monies, innocence must be established and not presumed.

If the initial review determines that a thorough investigation should be undertaken, the only satisfactory outcome for the accused is the presence of a verifiable set of primary data that support the practice or publication that has been questioned. Institutional oversight must assure that investigation of the alleged misconduct is promptly carried out in a rigorous manner.

CONCLUSIONS

Institutional oversight should strive to provide a supportive, interactive and collegial environment in which innovative research can thrive. Institutional standards must be clear and compliance with them should be carefully monitored. Emphasis should be on the responsible conduct of research rather than solely on procedures for investigation of alleged misconduct. □

By doubting we come to inquiry;
by inquiry we come to truth.

(Peter Abelard (1079-1142)

Informed Consent — How Much is Enough?

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ETHICAL BASIS OF INFORMED CONSENT

One of the most difficult tasks the research commitee faces is convincing clinical investigators that producing a carefully thought out, well-written consent document is an integral component of their research study. Too often the consent form appears to be a hastily tacked on attempt to appease bureaucracy. An understanding of the ethical basis of the research consent process and of its historical development provides convincing evidence of the necessity for a formally documented research consent.

Three fundamental ethical principles have proved to be directly relevant to discussions of moral problems encountered in conducting research.

1) *Respect for Persons* gives rise to guidelines on informed consent
2) *Beneficence* leads to examination of risks and benefits
3) *Justice* provides for a fair selection of research subjects

These principles have formed a foundation for the development of the ethical traditions of Western civilization.

It must be noted, however, that although all three underlying ethical principles are always applicable to human research, the perception of their relative importance may change with time and from one society to another. In North American society today, the primary ethical imperative in research on humans is *Respect for Persons.* In contrast, in some other Western societies, considerations of beneficence and paternalism are foremost. The principle of Respect for Persons requires that individuals capable of self-determination and free of external control be treated as autonomous agents. The obligation to obtain informed consent in clinicial investigations is based upon the principle of autonomy. Persons with diminished capacity, such as children and the mentally handicapped or persons subject to external constraints such as students or prisoners, are entitled to protection.

OVERVIEW OR HISTORICAL DEVELOPMENT

Informed consent in the research setting has evolved through a series of codes, statutes and regulations dating primarily from the mid nineteen forties. This is in contrast to informed consent for patient treatment which is based primarily on case law.

In the 1930s, Dr. Freiherr von Verschuer was a leading international figure in medical research. The *Journal of the American Medical Association* editorialised on the absolute necessity of research in his subject area; and in recognition of his work von Verschuer, in 1939, was invited to address the Royal Society. His lecture was entitled: *Twin research from Francis Galton to the present day.* Dr. von Verschuer was the director and founder of the Institute of Heredity and Race Hygiene at the University of Frankfurt. Dr. von Verschuer's research assistant was Dr. Jospeh Mengele, later appointed chief physician at Auschwitz. His studies at Auschwitz were supported financially by the German Research Society, and eyes of executed inmates were sent to von Verschuer for his research.

It would be comforting, but simplistic, to conclude that German researchers of that era were all ignorant, deranged, or sadistic. In 1931, Germany had enacted on moral grounds strict regulations to control human research. These regulations remained law throughout the Third Reich. They included legal requirements that consent must always be given "in a clear and undebatable manner". Ironically no other nation had such morally and legally advanced regulations and, a special irony, the 1931 regulations contained no less adequate protection than the Nuremberg Code which was the outcome of investigations into their abuse.

Nuremberg Code

The military judges at Nuremberg, in response to the revelations of German reserach atrocities, developed, with the guidance of expert witnesses, a universal standard of ethical research practices, the *Nuremberg Code.* In its first section the Nuremberg Code laid out the following clear-cut guidelines for obtaining consent for human research:

1) *Voluntary* consent for the human subject is essential. This means that the person involved should have *Legal Capacity* to give consent and should be able to exercise *Free Power of Choice.* There must be no element of force, fraud, or deceit.
2) *Knowledge*
3) *Comprehension* of the elements of the subject matter involved as to make an understanding and enlightened decision.

To help in achieving *comprehension,* the Code

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requires that before the subject is accepted into the study he is informed of the following:

1) The nature, duration, and purpose of the experiment;
2) The method and means by which it is to be conducted;
3) All inconveniences and hazards reasonably to be expected;
4) The effect upon his health or person which may possibly come from his participation in the experiment;
5) *the right to terminate participation*

Although the Nuremberg Code had no force in law, it served to stimulate public awareness worldwide and lead to the development of codes of ethics for research in a large number of countries.

Declaration of Helsinki

As national codes were developed independently, it eventually became evident that there was a need for an international restatement of common principles. In 1964, the World Medical Association adopted the *Declaration of Helsinki.* This document, revised in 1975, is an important international consensus on human research ethics but lacks the specificity of the Nuremberg Code.

The Nuremberg Code published more than forty years ago contains all the ingredients we recognize as essential today, for an informed consent. Although it provoked considerable international reaction and stimulated further examination of ethical principles in research, evidence indicates that many clinicial researchers remained ignorant of these basic subject rights. The mere presence of a code of research ethics, however widely publicised and however fresh the memories of atrocities, was just not sufficient to ensure ethical conduct of research.

Since Nuremberg there have been numerous exposures of unethical research, often conducted by eminent researchers and supported by major institutions. The classic expose by Beecher (*New England Journal of Medicine,* 1966) cites 50 examples. The following cases are among those which provoked considerable controversy and public outcry when they were exposed by the press and were instrumental in the development of U.S. regulations on human subject research.

Tuskegee Syphilis Study: A Public Health Service study commencing in 1932 and designed to study the natural history of untreated latent syphilis. A total of 400 black male subjects were recruited without informed consent and told in fact that some of the research procedures (spinal taps) were special free treatments. This study was carried on uninterrupted for 40 years, despite the availability of penicillin and despite a demonstrated 20% increase in life expectancy. Untreated subjects were systematically blocked from receiving available treatments. The study was only terminated in 1972 when first accounts of it appeared on the front page of the *New York Times.*

Willowbrook Studies: Under the direction of a leading infectious disease specialist, Saul Krugman, these studies were designed to investigate the natural history of hepatitis and to develop an effective prophylactic agent. Willowbrook was an overcrowded New York State institution for mentally handicapped children where poor sanitary conditions gave rise to endemic viral hepatitis. On the premise that they would probably contract hepatitis anyway, children were deliberately infected with hepatitis by being fed infective fecal or serum extracts. Consent forms mislead parents into believing their children were receiving a vaccine and coercion was alleged. Later in the study, due to overcrowding, parents were only able to get their children placed if they entered the hepatitis unit.

Jewish Chronic Disease Hospital Study: In this study live cancer cells were injected into debilitated non-cancer patients to study their rejection pattern. Naturally, patients were not told they were going to receive cancer cells for fear of frightening them unnecessarily. The idea of the experiment was to see if delays in rejection of cancer cells by cancer patients was due to their cancer or to their general debility, and patients without cancer were needed as controls. The study was funded by the Public Health Service and the American Cancer Society and served to bring to the fore a public awareness that the judgement of a clinical investigator cannot be the sole basis for the ethical conduct of human research.

ESTABLISHMENT OF THE RIGHTS OF THE INDIVIDUAL

In the last thirty years or so, there has developed an increasing awareness among the general population of the basic rights of an individual — particularly in North America. Human rights movements, patient's rights movements, the Canadian Charter of Rights, are all a reflection of the growth of our recognition of respect for persons — that is in this case their autonomous right to decide on whether or not they will participate in research. With this rise in recognition of the autonomy of the individual has come corresponding fall in the acceptance of paternalism. No longer is the presence of research risks the prime consideration in determining that informed consent must be sought.

Revelations, such as those described, lead to public demand in the U.S. for some effective control of human research. Years of intense U.S. Congressional interest in the ethical aspects of health care followed, beginning in 1974 with the enactment of the National Research Act. This legislation required:

1) All research in institutions receiving Federal funds to be submitted to an IRB (Institutional Review Board) for ethical review.
2) Regulations be drawn up to protect human subjects by law.
3) The establishment of a National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research: 1974-1978.

Today almost all human research in the United States is subject to the Federal Regulations and must be approved by an IRB. IRBs must adhere to strict legislative requirements and are subject to Federal inspection. In Canada, the Medical Research Council (MRC), in 1978, published guidelines on ethical standards for the use of human subjects in research. These guidelines were updated in 1987 and include the requirement of review by an REB (Research Ethics Board).

The question of whether guidelines or legislation would be more appropriate for regulation of human research in Canada was addressed by the MRC Standing Committee. It was felt that guidelines would be preferable and sufficient in the Canadian context. However, as history has shown, guidelines are of little use if they remain unread and unheeded. On the other hand, it is easy to see how the ethical perspective can be lost when the emphasis is on interpreting legal directives, as in the U.S. Regulations.

Having established ethical guidelines, what is the most practical approach to obtaining an ethically valid consent? First the research subject must be informed through the disclosure of a core set of facts or propositions. The consent form (or information sheet) is the written record of what the reasonable subject would need to know.

INFORMED CONSENT PROTOCOL

1) Project title
2) Identification of investigators
3) Invitation to participate
   - — participation is voluntary
   - — refusal will not affect the quality of care
   - — there is no penalty for withdrawal from the study
4) Reasons for the study (statement of purpose)
5) Basis for subject selection
   - — inclusion and exclusion criteria
6) Explanation of procedures
   - — expected duration of participation
   - — description of precedures

   Procedures should be described that are relevant to the subject. How much blood will be withdrawn, how often, where will the research be done, who will do it, how much time will be involved, identification of experimental design, particularly those features such as placebos and randominzation which are peculiar to research, emphasis on how treatment in research process will differ from regular clinical care
7) Description of reasonably forseeable risks and discomforts
8) Anticipated benefits to the subject or others
9) Disclosure of appropriate alternative treatments/ procedures and *the options for obtaining the same therapy outside the research setting*
10) Assurances of confidentiality
11) Contact for answering questions
12) The consent form should be signed by the subject and investigator, and the subject should receive a copy of the consent form

Despite 40 years of virtual consensus on what is required for valid consent, consent form problems are the major reason for failure to approve human research.

Reasons for Rejection of Research Proposals
(L. Bordsky, University of Illinois)

Administrative Problems	15%	missing letters of collaboration
Protocol Problems	33%	inconsistencies and ethical problems
Consent Form Problems	85%	poor presentation, terms too technical, information overload, incomplete information, misleading or incomplete description of risks and discomforts, misleading statement of benefits

Essentially, consent form problems can be reduced to two major areas: In both these areas the key to an effective informed consent lies in good communication between the investigator and the individual research subject.

Disclosure of Risks: *Research differs from medical practice in that the research subject, as a volunteer, must be informed of all known risks in humans. The benefits and risks must be weighed, and the ratio must clearly be favourable, for research to be ethical. The possibility of unforeseen risks must also always be raised.*

Essentially what the subject needs to know is the following:

What kind of risk? (nature)
How likely is it to occur? (probability)
How serious is it? (magnitude)
How long will it last? (duration)
Can anything be done to minimize the risk?
How effective will corrective action be?

It is important to remember that the research subject is a volunteer and as such may wish to know much more about the risks involved than a patient undergoing necessary treatment. While the consent form will provide the basic information on possible risks, potential research subjects will vary in what they regard as acceptable. The researcher must try to determine what more a research subject would like to know.

Traditionally, determination of risks involved in research participation has centred on physical harms. However, we are also encountering research with potential risks for social and psychological harm (fetal tissue research, genetic research, AIDS research).

Comprehension: It has been shown in a number of studies that information recall may be inversely correlated with length and complexity of consent forms. For this reason, it is imperative that research subjects be given a copy of the consent form. Even researchers supportive of the goals of informed consent may have difficulty deciding what subjects need to know in order to make informed decisions.

The inclusion in the consent form of material which cannot be readily understood by a lay person makes it difficult to show that an ethically (or legally) valid consent has been obtained.

BARRIERS TO EFFECTIVE CONSENT

A number of issues may more subtly affect the conduct of research and the validity of patient consent. These issues are now being brought more to the fore and concerns expressed in print by a number of leading researchers and ethicists.

Great care is now taken to protect vulnerable populations such as those exploited in past research abuses (children, mentally incompetent persons, prisoners). But there is the growing recognition that anyone who is patient is vulnerable. Howard Spiro, a noted gastroenterologist, sums up the 'Dependence' of the patient on the physician/reseacher thus: "They would swallow new drugs, receive infusions of calcium or glucagon, or even embrace esophageal or rectal catheters because they had faith in my good will or, as I now fear, they wanted to please me."

Based on lessons learned from past abuses, researchers are now beginning to examine their own motivations and the unconscious pressures that may thus be brought to bear on patients to participate in research.

Pressure to Produce: Grants and promotions often depend on successful research and recognition in the research community by publishing first about a new drug, technique, or discovery.

Messiahs: The overzealous pursuit of lofty research goals where the end justifies the means. Good science is not necessarily good ethics.

Sponsor Pressures: Care must be taken by the research to avoid inducing consent from the subject by the promise of reward. In commercially sponsored trials, the investigator (and the research committee) must also give careful consideration to the possibility of inducement to researchers through the promise of reward rather than acceptable compensation for a study deemed worthwhile. Pharmaceutical companies compete vigorously for available patients. For example, in trials of new ulcer drugs scarcity of patients resulted in reports of substantial bonuses for each patient who completes a study.

The ultimate ends of the research must also be taken into consideration. The "ethical; medical and scientific purposes" has to be carefully weighed (Medical Research Council of Canada Guidelines, 1987).

It is not only commercial sponsors who may provoke recruiting pressures. In some studies, including NIH sponsored cancer clinical trials, there are requirements for a minimal number of participating patients per institution for continued financial support.

EFFECT OF NEW TECHNOLOGIES ON PRESENT CONSENT PRACTICES

To date, not much attention has been given to those generalized consent forms used in most health facilities for routine blood and tissue sampling. Their wording is usually nonspecific, allowing the laboratory to utilize the sample as they see fit without notification of the patient. However, emerging laboratory technologies together with recent court decisions on the use of blood and tissue samples, indicate more attention must be paid to consents in this area.

Recombinant DNA technolgoy using patient tissues and fluids is now an active area of research in many medical institutions and may lead to lucrative commercial spinoff. The burgeoning biotechnology industry relies on the products of this research. Also looming large over the laboratory horizon is DNA sampling for genetic research on kindreds — for disease risk prediction — with all the possibilities this raises of infringements of individuals rights to privacy.

Illustrative of the problems that are already appearing is the case of John Moore, a victim of hairy cell leukemia, whose spleen was removed in 1976 at the UCLA Medical Centre. His discarded spleen was used for research and found to produce what turned out to be a profitable cell line. For seven years following the surgery blood samples were collected from him a regular intervals both to check on his progress and to fuel the cell line of which he apparently remained in ignorance. Ruling in the John Moore case, on July 21, 1988, the Court of Appeal of California stated that a "person's cells and genes are a part of his person". On December 8, 1988, the Supreme Court of Canada ruled that the use of blood taken from an unconscious (i.e. unconsenting) patient to gain information about him represented an invasion of privacy. The fundamental issue emerging from these decisions is that patients have the right to control what happens to their own bodies, including the uses to which tissues removed from their body are put if their identity is retained.

CONCLUSION

Ethically and legally the general obligation to obtain informed consent is clear; specific exceptions to this requirement must be ethically justified. How much is enough? The guidelines are well established and form a firm foundation upon which the researcher may build. □

Placebo-Controlled Trials in Terminally-Ill Patients

WHAT PLACE COMPASSION?

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I have been asked to address a special problem in the area of human research — research with terminally-ill patients. It is a pleasure and privilege to do that at this point in the program, particularly since we have already had the advantage of hearing Dr. Laycock's careful discussion of informed consent (a critical ethical question in any consideration of ethics vis-à-vis human research) and since we have already been greatly enlightened by Dr. Morgan's precise remarks concerning misconduct in design and implementation of research protocols (a subject most relevant, too, to any reflection about my assigned topic).

In a recent *JAMA* article, Dr. John Weg, an intensivist, commented that the prospective randomized double-blind placebo-controlled trial is of quintessential importance in resolving the often complex controversial clinical problem.[1] Scientifically speaking, such a trial is seen as providing the closest approximation to "truth" in the clinical research area. That being said, there are ethical concerns about its implementation with regard to any patient-subjects, and particularly those patient-subjects who are terminally-ill. Therein lies the problem for present discussion. My purpose is to sensitize to the ethical issues here, and to encourage resolution of them by way of reflection and discussion about them. In other words, this paper is to be understood as no more, no less, than an ethics discussion opener.

As a beginning, what (or who) do we identify when we speak of "terminally-ill" persons? According to one stream of current philosophic thought: since all human beings are mortal, all human beings are terminally-ill! In the more limited and immediate sense, however, we are able to identify persons who appear to be imminently, irreversibly, moribund; we say they are terminally-ill. We also make regular use of the term in describing another group of persons, i.e., those who have a disease which poses a significant threat of dying. Unless/until the course of their disease is promptly and significantly altered, these individuals, too, are clearly identifiable as fatally-ill. They may die sooner, e.g., the individual with late-stage AIDS or uncontrollable cardiac arrhythmia; they may die later, as the individual with early Alzheimer's disease, initial multiple sclerosis or certain of the neoplastic maladies at an early stage. Finally, we must also include those persons who suffer sudden severe trauma, predictable or not, e.g. those who have had a serious cardiac or cerebral insult which was not expected. To speak very generally, all such individuals appear to be "incurable"; they, and others like them, form the cohort, "terminally-ill patients".

It is well-understood that any potential cure for such individuals will be grounded, in the main, on the results of research concerning the etiology and course of their terminal illness. Is such research, that is, research which uses terminally-ill patients as research subjects, thereby justified? More particularly, is use of such persons in the placebo-RCT (randomized clinical trial), that 'gold standard of research', thereby justified?

Granted the noble goal here, those sensitive to the ethical dimension of the question will be concerned first with the vulnerability (physical, psychological, spiritual) of terminally-ill patients. Participation in a research endeavour is never risk-free; alternatives to the RCT will thus be sought so as to not subject those already at some disadvantage to the possibility of further disadvantage.

What options are available here?

Would retrospective review of patient-outcomes subsequent to use of certain therapeutic modalities be useful? Would comparative trial of several 'less good' treatments be helpful? Theoretically, either approach should pose less risk to this group of individuals at risk then trial-use of randomized placebo-putative therapeutic agent. Theoretically, either approach should also provide *some* new scientific knowledge.

But our assigned question sets such alternatives aside. For purposes of this discussion only, let us accept the view that these (and other) alternatives have been considered, and have been rejected here, for whatever reasons. What, then, about the ethics of the placebo-RCT, with the terminally-ill patient as subject? If the presenting situation is such that it is placebo-RCT, or nothing, then . . .?

A spectrum of ethical viewpoints is available for response to the more general question of use of individuals-at-risk as research subjects.

For example, some authorities will be negative to any research involving the dying patient. Recall one of the slides presented by Dr. Laycock; the response there, based on concern for the current status of such patients (apparently irreversible, life-ending illness, with all the spiritual and emotional vulnerability that entails) is resoundingly negative. No matter that science cannot advance in the absence of such research; these individuals are to be subjected to no additional risk.[2]

A somewhat less stringent view is espoused by Jonas who argues a descending order in choice of research

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subjects.[3] Thus, begin with the most able and most committed individuals (e.g., researchers themselves), leaving selection of the weakest individuals as research subjects to the last. Jonas has moved the discussion further towards open-research; patients-at-risk *may* be used as research subjects, albeit last, if certain conditions are met (e.g., they identify via consent with the research project for which no other individuals would be suitable). This position reflects concern for the vulnerability of these patients; it speaks to respect for them even as it does to concern for the progress of science.

A third point on the ethical spectrum is well-illustrated by reference to the now classic (U.S.) Tuskeegee Syphillis study[4] and to the recent New Zealand Cervical Cancer Study.[5] In the former case, certain syphillis-infected black men were observed, without intervention by way of available treatment, until their deaths — this as a way of charting the uninterrupted progression of the disease. In the more recent event, general practitioners referred women identified as having abnormal cervical cytological findings to consultants for the specific purpose of treatment during what was judged to be the pre-invasive stage of cervical carcinoma. Some, not all, of these women received treatment; none knew that the consultants had placebo-therapy randomized them; 22% of the untreated women developed advanced invasive cancer. Presumably, both of these endeavours were initiated in an attempt to further science first, with scant attention to the concerns of risk and consent voiced by those at the first and second points on the ethical spectrum described.

Taken collectively, the various positions noted here focus the debate in this area on the topics considered most important, ethically speaking. Scientific advance, consent as a mark of respect for person, and minimal risk, must all be balanced if use of individuals-at-risk as research subjects is to be ethically countenanced. Most importantly, and in need of careful justification, is the priority to be assigned to these various concerns.

To speak more specifically now in the placebo-RCT context.

For some commentators, choice vis-à-vis participation in a placebo-RCT is seen to be a necessary but insufficient ethical requirement. Among others, Dr. Robert Levine offers a negative reflection on this point, and that on grounds of risk of (earlier) death.[6] Thus, even though the subject may consent to be deceived (as it were), even though the subject has had putative risk/benefit explained, still the researcher has no right to ask individuals with certain serious illnesses to participate in a RCT which involves placebo-use. Levine's concerns are expressed in his discussion of clinical trials which involved individuals with peptic ulcer in one case, and individuals with a diastolic blood pressure of 115-129 in the other. He asked whether a placebo-RCT was justified when, for those not receiving a medication known to be effective, there was a 1.5% risk/year of disabling complications in the first case and a 28% risk/year of severe complications of death in the second case. Ethically speaking, even though the population might benefit from this type of placebo-RCT, even though the chosen subjects might consent, Levine argues that such research ought not be done. Use of the placebo in such cases is not only non-therapeutic (that *might* be allowable, with research-subject consent); it also poses more than minimal risk (when those who require a known medication are deprived of it).

There is a still more troubling discussion of such research to be considered here. If the putative research subjects are terminally-ill, then, presumably, they are patients. In the situation of medical care, the physician is obligated to put the patient's interests first. This is the common expectation of the profession and of patients. Presuming the outcome of any research-effort is unknown in advance, how can the physician argue that participation in such a trial is in the patient's best interest?

To justify enrolling such a patient in this kind of trial, the physician must personally be in a genuine state of uncertainty as to the efficacy of any known treatment; thus, participation in the research trial is the best that can be done for the patient in question. According to Freedman,this same argumentation would apply when a more generally-judged state of 'clinical equipoise' obtains with regard to several possible therapeutic modalities vis-à-vis an indentified clinical problem.[7] In that situation, the physician may choose to recognize the profession's general uncertainty in the matter at hand, and thus elect to place the patient in a clinical trial as the best possible action, this according to the judgment of the profession as a whole. Of course, having done this, if the physician becomes convinced that such participation is no longer in the patient's best interest, then, as is well-recognized, the interest of the patient is to take priority over any interest the physician might have in the advancement of science via the patient's participation in the research protocol.[8]

If research-participation for patients, generally speaking, can be justified on this ground of general 'clinical equipoise', are there any particular problems with the use of the patients of concern here, i.e. patients who are terminally-ill? History provides some illumination on this point.

It may be, for example, that certain 'medications' are available only, and then only as a randomized possibility, for those agreeing to participate in the placebo-RCT. The terminally-ill patient who is desperate for a chance to receive the 'medication' may falsify symptoms or medical history so as to be considered for participation in such a study. The physician, pressured by what the patient (or physician) sees as last or only hope may be moved by compassion to acquiesce with the patient's desperate desire to enroll in such a study (or may suggest it, out of a feeling of personal desperation/futility). Such patient participation is understandable in some sense of 'humane' medicine; at the same time, such participation

may jeopardize the scientific accuracy of the study, particularly if the patient-subject not randomly-assigned to the study's 'treatment arm' choses to leave the study-group before the protocol is completed. For the physician, to knowingly abet such patient behaviour is again understandable in some sense of 'humane' medicine; at the same time, it is to thwart the pursuit of scientific knowledge which forms the recognized basis for medical practice.[9]

Potential conflict of interest problems can also be envisaged here, presuming the 'medication' in question is unavailable on compassionate grounds and the patient and physician disagree about enrolling the patient in the placebo-RCT. If the patient is judged by the physician to be a 'suitable' research subject, and wishes participation, albeit on grounds of desperation, and the physician is not personally in a state of clinical equipoise, or is unwilling to identify the profession's view as uncertain . . .? Obviously, the patient must then 'shop' for another physician. Or if the physician recognizes participation as the only possible avenue for access to the 'medication', and the patient is a suitable candidate but the patient refuses participation . . .? The physician may (or may not) lose the patient to the terminal-illness; certainly it is an opportunity missed to contribute to the advancement of scientific knowledge about the disease in question.[10]

Moving from historical and theoretical contexts to the contemporary situation, what about ethical opinion vis-à-vis research use of the HIV+/AIDS patient, e.g.; should these terminally-ill individuals be enrolled in placebo-RCTs?

Again, there is a spectrum of ethical opinion.

Krim, e.g., asked in 1986 that patients with full-blown AIDS have opened access to any therapy of promise.[11] This was argued, not because of the wish that the drug in question might work, but on the grounds that "the patient has the right to fight for life with whatever tools it can offer". Thus, at one end of the contemporary HIV+/AIDS spectrum, full availability is sought, this despite the lack of demonstrated scientific validity of certain of the 'medications' in question, and this because of the patient's claim to self-direction as well as interest in self-preservation. Some such thinking is present in the recent IND rules in the U.S.,[12] as it was in the decision of (Canadian) Minister of Health Beatty who has now announced a wider availability of AZT to more HIV+ and AIDS patients.[13] This same thinking prevails among those seeking more availability of DDI — a possibly useful 'medication' for treatment of HIV+ and AIDS patients, made in Canada for distribution only outside Canada.[14] And the same thinking characterizes the statements of many individuals within groups, e.g., the Vancouver People with AIDS Coalition whose chairman has argued that "people should have the right to make their own decisions".[15]

Since, as already noted, desperate people will undertake desperate means to achieve their chosen ends, it is quite possible that some researchers will restrict access to trials for such desperately-ill people to those willing to pay large entry fees. Consider, Biotherapeutics Inc. in Tennessee; this group is reputed to be willing to let such persons receive the 'newest possible drugs' in the agency's 'trials' of cancer treatment, presuming these persons pay fees reported to exceed $30,000.[16] This may be to honour patient's choices — it does so at a very high price.

Following on such a concern, it should also be noted that the medical profession and the government have a duty to protect all victims of disease from further harm.[17] Such argumentation could be used to justify restriction of 'medication' to the approved variety, or to that available within the placebo-RCT. Further, there is concern that longrange scientific advances, for the good of future terminally-ill patients and their society would be jeopardized if non-scientifically validated 'medication' were made available now. Indeed, who would choose to be a research subject if the 'medication' were otherwise available? Some fear that desperate patients will be incapable of assessing the risk attached to use of improperly (or non-) tested 'medications'. Others are uneasy about current costs in connection with distribution of untested 'medications'; the costs of possible failure may be considerable should these current 'medication' not be appropriate.[18]

How are these contrasting sets of concerns to be harmonized? Is patient choice to prevail? Should we set aside uneasiness about possible harm and non-advancement of science? Is the professional and governmental obligation to prevent harm to reign supreme here, this in tandem with affirmation of the need for longrange scientific progress?

Ethical response to an ethical dilemma must begin with examination of possible alternatives. Among alternatives appropriate to this situation:

1) Can stopping rules relevant to statistical accuracy for the pertinent placebo-RCT protocols be eased in some way, while yet maintaining an acceptable level of scientific validity?
2) Is there a way to conduct retrospective trials of any 'medications' already dispensed to terminally-ill patients on compassionate grounds?
3) Is there a way to randomize use of newly-developed and newly-developing drugs by terminally-ill patients, even as they are applied in compassionate use?[19]

Other alternatives could no doubt be adduced; none seems presently available. Each of those listed here brings into question the current reliance on the placebo-RCT research strategy as quintessential. The observations of Dr. Soskolne, a Canadian epidemiologist, well-known for his work on AIDS, seem more apt here than those of Dr. Weg, noted earlier. To quote Dr. Soskolne: "The time may have arrived or soon be upon us where the dignity and the claim of life of the human subject and our own concerns for both morality and ethics have to outweigh our determination to contribute to the

continued advance of knowledge and hence of human health".[20]

At the conclusion of this discussion-opener, and in most general terms, there appear to be but two choices available in resolution of that most extreme example of ethical dilemmas as presented by use of terminally-ill subjects in placebo-RCT protocols.

Alter the current scientific approach in the name of current 'humane-ness'; adhere to the current scientific approach, favouring longrange, over current, 'humaneness'.

The values at issue here have been carefully identified: choice, minimal harm, scientific advancement. Once the relevant facts have been clarified, sound ethics methodology requires that a decision be made among the (altered ?) choices available.

Whichever of the two options is chosen with reference to use of terminally-ill patients as subjects in the placebo-RCT, the contemporary meaning assigned to 'compassion' will have changed.

But it is time now for the discussion to begin . . . □

Notes

1. Weg, John G. Critical Care Medicine. *JAMA* 1989; **261:** 2836-7.
2. Cf. Public Health Council of the Netherlands. *Report on Human Experimentation*, summary published in *World Medical Journal* 1957; **4:** 299 at #6h.
3. Jonas, H. Philosophical Reflections on Experimenting with Human Subjects. *Daedalus* 1969; **98:** 219-247.
4. United States Tuskeegee Syphilis Study Ad Hoc Advisory Panel. *Final Report*. 1973; Washington: Public Health Service.
5. Paul, C. The New Zealand Cervical Cancer Study: Could It Happen Again? *BMJ* 1988; **297:** 533-9.
6. Levine, Robert J. The Use of Placebos in Randomized Clinical Trails. *IRB* 1985; **7:** 1-4.
. . . Referral of Patients with Cancer for Participation in Randomized Clinical Trials. Ethical Considerations. *Ca-A Cancer Journal for Clinicians* 1986; **36:** 95-9.
7. Freedman, B. Equipoise and the Ethics of Clinical Research. *New Engl J Med* 1987; **317:** 141-5.
8. Medical Research Council of Canada. *Guidelines on Research Involving Human Subjects* 1987. Ottawa; Minister of Supply and Services, Canada: 9.
9. Vanderpool, H.Y. and Weiss, G.B. False Data and Last Hope: Enrolling Ineligible Patients in Clinical Trials. *Hastings Center Report* 1987. April; 16-19.
Simon, R. and Wittes, R.E. Methodologic Guidelines for Reports of Cancer Trials. *Cancer Treatment Reports* 1985; **69:** 1-3.
10. Cf. Taylor, K. et al. Physicians' Reasons for Not Entering Eligible Patients in a Randomized Clinical Trial of Surgery for Breast Cancer. *New Engl J Med* 1984; **310:** 1363-7.
11. Krim, M. A Chance at Life for AIDS Sufferers. *New York Times* 1986; August 8: A27.
12. United States Department of Health and Human Services, Public Health Service, Food and Drug Administration. *Investigational New Drug, Antibiotic and Biological Drug Product Regulations; Treatment Use and Sale* 1987: 21 CFR Part 312 [Docket No. 82N-0394] Rockville, Md.
13. Taylor, P. Ottawa Widens Access to AIDS-Slowing Drug. *Globe and Mail* 1989; September 7: 1.
14. Taylor, P. Canadians Can't Get AIDS Drug Made in Edmonton. *Globe and Mail* 1989; September 8: A3.
15. Cf. Note 13.
16. Pay-your-own-way-research. *Newsweek*, Feb. 9, 1987: 61.
17. Cf. Note 13.
18. *ibid.*
19. Cf. Kessler, D. The Regulation of Investigational Drugs. *New Engl J Med* 1989; 320,5: 281-8.
Freedman, B. and The McGill-Boston Research Group. None Validated Therapies and HIV Disease. *Hastings Center Report* 1989; **19:** 14-20.
20. Soskolne. Scientific and Ethical Conflicts in Cancer Studies Involving Human Subjects. *Women and Health* 1986; **11:** 197-215.

Fetal Tissue Transplantation for Parkinson's Disease

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I would like to address some of the technical issues involved in the use of fetal tissue transplantation as therapy for disease.

The first question that needs to be addressed when we consider the use of fetal tissue for transplantation, is why do it in the first place? What are the advantages of using fetal tissue as opposed to, for example, cadaver organs? There are essentially two key advantages that are decisive. One is the ability of fetal cells to continue their growth, and the second is the ability of fetal cells, at least in some circumstances, to proliferate. In various adult tissues those capacities are lacking. Of special interest in this regard are central nervous system disorders. The ability of the central nervous system to recover from injuries is, in most instances, quite limited: there is, in the adult, no production of new neurons. Furthermore, the ability of existing neurons to regrow their axons after damage is limited. As a result, functional impairment resulting from degeneration or destruction of the central nervous system tends to be unidirectional: some very important neurodegenerative diseases such as Alzheimer's and Parkinson's diseases progress inexorably.

Fetal tissue transplantation may be applicable also to other CNS disorders such as epilepsy, stroke, and Huntington's disease. Parkinson's disease, however, is the best test case for fetal transplantation, chiefly because the pathology is fairly limited. That is, the disease occurs when a particular population of cells — the dopamine-secreting cells of the substantia nigra — degenerate, leading to loss of dopamine input to the basal ganglia. The rest of the circuitry involved in initiation and coordination of movement appears to be relatively intact, so that patients' function might be substantially improved if we could restore this dopamine input to the basal ganglia.

There is now a very large body of studies on animal models of Parkinson's disease, involving destruction of these dopamine-secreting cells. In Parkinsonian rodents, it has been possible to restore most measures of movement to normal levels by transplantation of dopamine-secreting cells from the ventral mesencephalon (the substantia nigra precursor). It is interesting that these transplants are not an exact reconstruction of the normal system. It has not been possible, so far, to obtain functional recovery by putting these grafted cells directly back into the substantia nigra, presumably because the grafted cells cannot grow axons the entire distance toward the basal ganglia. Instead, cells are transplanted into the target area, the basal ganglia, where they appear to establish normal projections and to release dopamine in a functionally-appropriate manner. More recently, a number of groups including my own have exended these rodent results, observing that experimentally-induced Parkinson's disease in monkeys can be at least partly alleviated by transplantation of fetal primate cells into the basal ganglia.

Very recently, these results have been extended to patients. Initially, such clinical procedures were attempted by transplantation of adrenal tissue. These were autografts of the patient's own adrenal medullary cells to their basal ganglia. The chief motivation for this procedure was to avoid perceived social and ethical problems in the use of fetal tissue. However, the scientific rationale and the experimental justification for such adrenal procedures have always been ambiguous at best. The use of juvenile adrenal cells has been partially effective in rodents, but adult or aging adrenal tissue has been less effective. In clinical trials, it appears that only a small fraction of the patients thus treated have any significant recovery. In those patients it is not clear to what extent the grafted tissue, itself, is involved in that recovery. The evidence for the success of fetal tissue in adults and animals is much more persuasive. In humans these experiments have only been done in the last two and half years and we simply do not have enough data. In most patients where evidence has been reported at conferences, the results are overwhelmingly positive and encouraging for the use of this procedure.

With this background, let us consider the proposed clinical trial of fetal transplantation at Dalhousie University and the Victoria General Hospital. Our research protocol was first presented to an ethical review committee of the Faculty of Medicine for approval of the laboratory component of the research. After the Faculty of Medicine review and approval, the protocol was submitted for approval by the Research Review Committee of the Victoria General Hospital. After their review and approval came review by the Medical Executive of the hospital, subsequent review by a hospital Ethics Committee, and finally review by the Board of Commissioners. The review procedure is now complete: approval has been granted, by all these groups, so that actual clinical implementation can now be done.

It is, I think, of interest that during this review process there have been pressures applied not only in the public forum in the context of newspaper articles and letters, but also by letters sent to members of the review committees including, for example, threats from

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Dalhousie Medical Alumni to discontinue their donations to the University if our research were permitted. It is worth mentioning that extensive hearings in the United States and the United Kingdom by government commissions on ethical aspects of fetal tissue transplantation have without exception led to strong endorsement of these fetal transplant procedures.

Let me now present some of the objections that have been raised to the use of fetal tissue transplantation for the treatment of neurological disorders and attempt to respond to them, at least briefly. Objections to the use of fetal tissue transplantation are usually objections to the abortion procedure itself. Most of the procedures which have been described have involved the use of tissues from elective abortions, but it has been suggested that spontaneous abortions would provide an adequate source of tissue. This, however, is not a satisfactory alternative, since in the overwhelming majority of cases the tissue from spontaneous abortions is pathological, being contaminated or ischemic or suffering from some other dysfunction which would render it not useful for transplantation.

Another alternative that has been proposed has been the use of engineered cell lines. At the moment, this is not a satisfactory alternative because all available such cell lines are transformed so that their transplantation might form tumours. This is, however, an approach which may have promise in the future. A number of groups, including ours, are in the process of developing engineered cell lines that would have the biological capabilities of interest, and whose proliferation could be irreversibly suppressed. At the moment this is only a theoretical possibility, certainly not a superior alternative to the use of fetal tissues from elective abortions.

The next set of objections have to do then with the effects of the procedure on the fetus itself: that the collection of the tissue involves the causing of pain to the fetus, that it may be an affront to the dignity of the fetus, and that collecting the tissue and using it in such procedures involves killing the fetus. It has also been asserted that the use of fetal tissue for transplantation can provide an incentive for abortions that might otherwise have not been carried out. These objections and several related objections need to be addressed in the context of what we and other people are proposing to do. Our proposed procedure involves using tissue collected from abortions carried out independently, without reference to possible therapeutic use of the tissue. The tissue would be collected and prepared only after the abortion has been carried out. Collection and preparation of tissue would be performed on materials from fetuses which are therefore already dead and which have, in fact, been disrupted by the abortion procedure itself.

Perhaps most significantly of all, the tissue, if not used for these therapeutic purposes, would invariably be disposed of. In my opinion, and in the opinion of all the reviewing bodies that have considered the issue, what we have is a choice between the disposal of tissue on the one hand and its use for medical therapy on the other. In such cases where the abortions are occurring for presumably independent reasons and where there is no relation between the therapeutic use and the decision to undergo the abortion procedure, the opinion of the Review Committees has been that transplantation of such fetal tissue is ethical. I do not mean to imply that there are not many open questions involving such procedures, but most of the questions that remain involve details of the administration of such procedures and not the ethics of the procedures themselves. For example, it has been asserted that the widespread use of fetal tissue transplantation will lead invariably to commerce in fetal tissue, which would be morally repugnant. My response to that assertion is that at the moment there is no evidence for this: the availability of tissue from currently-performed elective abortions far exceeds likely use of such tissue in the foreseeable future. Furthermore, there is no clear reason why such commerce could not be legislated against should it emerge. I has also been objected that women might become pregnant just to supply tissue for the use of transplantation. However, as the procedures are currently planned, there would be no guarantee that the appropriate tissue could be prepared from a given fetus, so no one becoming pregnant with this goal in mind could be assured the fetus would have their intended use. Furthermore, a perceived advantage of targeted donation, mainly the absence of graft rejection, is apparently not relevant to neural transplantation, since major histocompatability antigens are not expressed on neurons.

I hope I have left with you a sense that there are ethical issues as well as legal issues that remain open and need further discussion, but that none of these mitigate against the use of fetal tissue transplantation, per say, or against the currently proposed procedures of using fetal tissues to help patients suffering from Parkinson's disease. □

The Challenges of Fetal Ethics

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The 1980s have seen enormous advances in genetics and biology. Knowledge has been greatly advanced and tools have been developed to provide insight into the wonders of human growth and development. Our capability for intervention in this process is developing rapidly. These interventions have potential for good and harm.

Good medicine is concerned, not only with immediate benefit, but with the whole person and societal good. Physician scientists play a major role in shaping and responding to societal values. Difficult choices are an integral part of medicine, concerned as it is with the health and the good of the patient. It is appropriate and necessary for researchers to reflect on the ethical issues involved in their work. Research involving the human fetus presents many fundamental issues of values and value conflicts.

The current controversy relates to the proposed use of human fetal adrenal from electively aborted fetuses for the treatment of adults with Parkinson's disease. This issue has met with sometimes heated debate. The language and tactic of the controversy can generate frustration and anger in the scientists. An unacceptable response is to conclude that the controversy is only at the "fringes" of public opinion so the scientists can decide for themselves the "right" thing to do.

Medical science does not exist in a vacuum. The pragmatic ethic that drives most medical science is insufficient to answer some of the profound questions of value and choice presented by contemporary knowledge and technology. Ours is a pluralistic society but this does not mean that medical science is value free. Research must constantly reflect on its values and choices.

Fetal ethics is the broader context for the consideration of the use of fetal tissue. This context requires reflection and consideration in four major areas:

1) Research — Therapeutic and Non-Therapeutic

What are the legitimate limits of non-therapeutic research on developing embryos and fetuses? Are electively aborted fetuses subjected to research, which would be unacceptable for other fetuses? Scientists cannot dismiss the method of tissue procurement as irrelevant. Consent has properly become an important issue in human research. Appropriate consent is an issue here.

Who consents to research on the fetus? Even with parental consent, are there restrictions on what can be done to fetuses and embryos? Is the fetus simply human tissue? Recognizing that personhood is a philosophical and not a biological concept, are there ways in which the fetus is distinct?

The present polarization on basic issues — if the fetus is a person then deserving all rights and considerations, if not a person then deserving no rights or consideration — is hampering seriour reflection. The potential for fetal experimentation is expanding and these issues must be addressed if this research is to be done well.

2) Fetal Therapy

Major therapeutic interventions on fetuses and embryos are being developed, and criteria for them need to be developed. If the fetus has any inherent value, then it has some right to medical treatment if such is available. As therapies become available there will need to be a process for decision-making with reflection on the fetal as well as the parental benefits.

If there is a choice between therapeutic intervention and therapeutic abortion for a "defective fetus"; the process of decision-making must be clarified. If the developing fetus has, at least, some right to a healthy intra-uterine environment, if the fetus has some meaning distinct from that which the mother determines, the nature of that right needs to be explored.

The MRC guidelines and the proposed revision of the law reform commission of Canada make it a crime to harm or mutilate a fetus. However, it is not a crime to abort. Questions of fetal therapy and experimentation can not be separated from the larger question of fetal rights.

3) Maternal/Fetal Conflict

As interventions on the developing fetus become more powerful, there is potential for conflict. Already, decisions have been made to prolong the life of a "brain-dead" mother until the baby was viable because that was the wish of the family. Charges have been laid in some American cases against women who took drugs during pregnancy. These are examples of maternal/fetal conflict. Is a father obliged to provide a healthy environment for a developing fetus? Is a mother obliged to abort a defective fetus or to treat one? Resolution of these issues requires serious reflection. Dismissal of the ethical issues as "fringe" positions in society does a disservice to both society and science.

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4) **Fetal Transplantation**

Can a scientist abstract completely from the source of the material upon which he or she performs research? Is there any other issue in which the method of procurement is irrelevant? What is the fundamental ethic that underlies the procurement? What are the values about therapeutic abortion which might affect the use of fetal tissue? The language is imprecise. The language of womens ' rights approach to abortion as simply a matter for the mother does tend to use the language which suggests the fetus is the woman's body and she has the right to absolute control. Clearly the fetus and fetal tissue and organs are NOT the mother's body. If this were not a genetically distinct organism with the possibility for differentiation, migration and proliferation, it would not be sought. The mother's organs are not being donated! The language must be clear. The fetus is a distinct human organism that would proceed to independent existence if the pregnancy were not interrupted.

Here, the mother gives permission for the tissue to be donated. The propriety of maternal consent is one of serious concern. There are individuals who argue that the mother relinquishes her rights over the fetus after an elective abortion. The transplanted fetal tissue may do another good. The question of whether the end justifies the means is a reasonable one. For what benefit or scientific advance or clinical efficacy is use of a human for another justified. Outcome in the recipient must be sufficient to justify the consideration of use of one human for another. The science must be valid before the ethical dilemma can be weighed.

There are a number of ethical issues with the use of fetal tissue in transplantation. Some of these issues needing elucidation are:

- *Injury to the fetus,* by the abortion, should not become compounded by more injury after the abortion. It is not sufficient to say the fetus is already dead or nonviable, therefore, another intervention is of no consequence. There is a separate decision when that transplant decision is made: 1) the question of valid consent for non-therapeutic interventions must be reviewed and procedures clarified. Biologic integrity is as important for the developing human as for the mother. 2) the consequence of an act is important. There may be the intention to do good but the act itself may have consequences that are bad or harmful. The societal implications of fetal transplantation may be profound for good or evil. Biologic viability is not the major issue. Genetic diagnosis and treatment on pre-implantation embryos is altering the time frame for interventions and the issues.
- There are legitimate questions about *scientific validity* in human research. The risk: benefit ratio must be explored in human terms.
- Researchers who desire to use fetal tissue to do good for the individuals who have Parkinson's Disease are an example of the dilemma that is frequently seen of individual need and *individual dignity* versus collective need and *collective dignity*. There is a larger issue at stake in how research looks at individuals as opposed to the societal good. In a society strongly motivated by an individualistic ethic, the common good may be more difficult to appreciate.
- Transplantation raises profound questions about *the definition and value of life and death.* Death has been redefined because of the technology. With the developing fetus, the need to extract usable scientific material may alter these definitions for the fetus. This altering of fundamental definitions has already been seen in the debate concerning the use of anencephalic fetuses as donors.
- *The value and status of the fetus* is still undetermined in this country. Is the only value of the human fetus because the mother of that fetus determines it has some? Is there a larger social and scientific context that recognizes this is a unique genetic individual in need of some definition of rights and recognition?
- *Ethical reflection* is required on the deeper meaning within the demands of scientific and technological excellence. There is at present *no public ethic in this matter.* This is a pluralistic society but without common values on fundamental questions there is no civilization! The values of family, children and reproduction are changing. Medical science both responds to and shapes these values. Each decision about the fetus affects these other realities in some way. The issues that are presented and discussed in this Research Day are significant. The medical community needs more reflection as our technology has outstripped our thought. The power of medical science is great; the values involved are greater. □

CURRENT TOPICS IN COMMUNITY HEALTH
Continued from page 138.

Comment:

This survey indicates that driving after drinking is pervasive in Canada, especially among young males. Physicians who routinely question their patients, "In the past year, have you ever driven after having two or more drinks in the preceding hour" may be able to provide information about alternatives to this high risk behaviour. Since drinkers are motivated not to drive primarily through fear of accidents or police encounters, people who do drive after drinking may have an alcohol problem. In fact, problem drinking is often identified through an impaired driving conviction. □

On Clinical Epidemiology, Classical Epidemiology and Chest Disease

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The last two decades have seen the emergence of "Clinical Epidemiology" as a "new" scientific discipline, one that is gaining in popularity among clinicians and epidemiologists alike. While completing my training in chest disease, I had the opportunity of receiving some formal post-graduate instruction in epidemiology, in a university department which, although decidedly "classical" in its outlook, was beginning to seek more interaction with the clinical disciplines. Through this experience, I was able to gain a new appreciation for the very useful place that epidemiology has in providing a framework for the activities of the academic physician as clinician, teacher and clinical investigator. Although my own training and personal bias lead me to frame these comments in the context of chest disease, it is obvious that both classical and clinical epidemiology have fundamental roles to play in all areas of medicine.

CLASSICAL EPIDEMIOLOGY — HISTORY AND DEFINITION

"Classical Epidemiology" is traditionally defined as "... the study of the distribution and determinants of diseases and injuries in human populations."[1] Its roots lie in the fields of mathematics and probability, ecology, and the public health movement. In its infancy, epidemiology was concerned largely with the cause and prevention of the communicable diseases that were then among the major scourges of society. The early control of pulmonary tuberculosis through public health measures thus provides an historical precedent for an intimate relationship between epidemiology and chest disease. With the successful control of infectious diseases, the emphasis of much epidemiologic activity then shifted to the chronic and neoplastic diseases wherein chest disease again proved to be fertile ground for study, as illustrated by the series of case-control and cohort studies establishing a link between smoking and lung cancer in the 1950s.[2,3]

One of the fundamental uses of classical epidemiology then, is as a form of population "book-keeping", describing and comparing the health status of large groups of people. The disparities and similarities between populations arising from such observational studies enable the investigator to formulate hypotheses concerning disease causation, and thus, the means of prevention. Hence, it was the epidemiologist who first postulated that tuberculosis is a communicable disease, but it was Robert Koch, a bacteriologist, who identified the tubercle bacillus. Similarly, while epidemiological work first suggested that smoking was causally related to lung cancer, it is left to biomedical research to identify with precision the carcinogens present in cigarette smoke. Although the latter, laboratory bench oriented activities are of great importance, we must remember that the elucidation of the specific causal factors is not critical to our ability to draw inferences from the epidemiological observation.

A more eloquent expression of this idea is found in an essay that recently caught my attention: "Of late years, conservative opinion does not allow anything to be really considered as 'etiology' unless we can succeed in getting it into a test tube, unless we can precipitate it, unless we can crystallize it, as it were. This is due of course to our current methodology which has perhaps become more of a religion than most of us realise. I think it may have led to a slightly narrow interpretation of clinical investigation ...."[4] These would appear to be timely comments given our collective fascination with "the current methodology" (molecular biology and immunology, now, I suppose), but in fact these words were written, and spoken, more than fifty years ago, by the late John R. Paul, in his President's address to the thirtieth Annual Meeting of the American Society of Clinical Investigation.

CLINICAL EPIDEMIOLOGY — HISTORY AND DEFINITION

It was Dr. Paul, a Professor of Medicine and Epidemiology at Yale University, who in the same talk fifty years ago first coined the term "Clinical Epidemiology". His plea then was for clinical researchers to move out of the laboratory and into the patient's environment, and he proposed "Clinical Epidemiology" as a new science "... concerned with the circumstances ... under which human disease is prone to develop, ... a science concerned with the ecology of human disease".[4] He noted that the fundamental difference between the old "orthodox" epidemiologist and the new "clinical" epidemiologist was that while the former "... dealt dispassionately with large groups of people, obtaining his results from the multiplication of observations ...," the latter "... must of necessity deal with small groups of people, groups no larger than a family or small community."[4] The clinical epidemiologist "... starts

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with a sick individual and cautiously branches out into the setting where the individual became sick: the home, the family and the workshop." Moreover, he emphasized the role of the clinician in performing this kind of research, commenting that "... if these fields are eventually to be investigated, it is the [person] with clinical judgement who can best blaze the trail, for it is prime responsibility of the clinician to do the work."[4] Finally, Dr. Paul spoke of the pre-eminent need of the clinical investigator to acquire attitudes in preference to techniques: "... still more important for the clinical epidemiologist than questions of technique and uniform, is his point of view. From the onset he cannot accept as Galenic truths, all the creeds, all the rituals of medical research that the generation just preceeding his, has professed...".[4]

In his 1938 address, Dr. Paul was in fact calling for more clinical investigation in the area of preventive medicine. Although his term "Clinical Epidemiology" has since taken on a broader meaning, the essence of what he said — the application of epidemiologic methods to the study of individuals or small groups, the transposition of knowledge acquired from populations to the clinical decision making process, and the central role of the clinician in generating relevant clinical research of an epidemiologic nature — is still germane to what has come to be known as "Clinical Epidemiology".

Clinical epidemiology re-surfaced as a distinct discipline, bridging classical epidemiology and clinical medicine, in the late 1960s, largely from the efforts of Alvan Feinstein of Yale University, and David Sackett, the founding chairman of the Department of Clinical Epidemiology and Biostatistics at McMaster University. Dr. Sackett, in 1969, defined clincial epidemiology as "... the application of epidemiologic biometric methods to the study of diagnosis and therapy be a clinician who provides direct patient care."[5] Although some have criticised this definition because it neglects the study of etiology (which may influence clinical decisions), and fails to encompass those measures of disease prevention or early detection that may be effective in individual clinical practice, the emphasis on the "... clinician who provides direct patient care ..." seems correct.[6] It is, after all, the clinical activities that take place at the bedside or in the physician's office — the observation, examination, and investigation of patients, and the responsibility for making the clinical decisions that affect their care — that require guidance, and that, as such, should provide the context for clinical epidemiologic research.[6]

W.O. Spitzer, chairman of the Department of Epidemiology and Biostatistics at McGill University, defines clinical epidemiology as "... the study of determinants and effects of clinical decisions," and points out that it is "... not merely epidemiology done by clinicians, nor does it pertain to the clinical activities of medically trained epidemiologists."[6] The clinical epidemiologist has a dual orientation, arising from both clinical medicine and epidemiology: he is usually an individual well trained in clinical medicine, who after receiving appropriate instruction in epidemiology and biostatistics, continues to spend the bulk of his time in direct patient care.[5] The initial fear, felt by some classical epidemiologists, that the addition of the prefix "clinical" somehow signified a dilution of their discipline, is effectively dispelled by Dr. Spitzer's remark that "clinical epidemiology is less likely a sign of compromised rigour than the mark of judicious focusing."[6]

CLINICAL EPIDEMIOLOGY — "A BASIC SCIENCE FOR CLINICAL MEDICINE"

Dr. Sackett refers to clinical epidemiology as a "basic science for clinical medicine."[7] Like the other basic sciences, it is not confined to a single body system or defined by such patient characteristics as age or sex. Its appeal to clinicians lies in its breadth of scope, its flexible boundaries, its sense of immediate relevance to clinical medicine, and its accessibility and portability. As a basic science, it is attractive to those who wish to pursue careers in academic medicine because it provides a foundation for each of the three major spheres of activity of the academic physician: clinical practice, education, and research. Moreover, for the chest physician, the historical ties between chest disease and classical epidemiology provide a background of tradition upon which new links between chest disease and clinical epidemiology may be forged.

CLINICAL EPIDEMIOLOGY AS A BASIC SCIENCE FOR CLINICAL INVESTIGATION

Clinical epidemiologic research pertains to the improvement of clinical decision making.[6] Because the clinical epidemiologist works in the vanguard of clinical medicine, he is well situated to pose questions that have immediate clinical relevance. Because he is also trained in research methodology, he can design clinical studies that are both valid and generalisable. His research is thus executed to provide himself and his colleagues in clinical medicine with answers they can apply directly at the bedside. "From question to application", as Spitzer says, "... the loop is tight".[6] The classical epidemiologist, though well versed in methodology, may not always have enough medical training or clinical exposure to be able to ask the most clinically relevant questions; similarly, although the "pure clinician" usually knows which questions need answers, he is prey to the pitfalls of poor study design.

What are the questions to which clinical epidemiologic research is best suited? By and large, they arise from the common issues that regularly confront the clinician responsible for making decisions about patients. Fletcher and Fletcher have organised these issues into the following categories: normality and abnormality, diagnosis, frequency of disease, risk, prognosis, therapy, and causation.[8]

1. Questions of *normality* and *abnormality* address our skills at clinical measurement, and how we separate true

abnormality from variation within the "normal range". It has been suggested by some that it may at times be useful to define abnormality in terms other than simply a measurement's proximity to the 5th or 95th percentile.[9] For example, a value for a given laboratory test may be taken as "abnormal" only if it is that which has been shown to be consistently associated with a disease state. In an even more stringent sense, an abnormal value may be taken as one which, if treated, leads to a better outcome. In this regard, one might say, for example, that only PaO_2 of less than 55 mm Hg is abnormal in the setting of chronic airflow limitation, since we know from a randomised controlled trial that treatment with continuous low flow oxygen in that circumstance leads to improved survival.[10]

2. Questions concerning our *diagnostic* abilities usually lead to the study of the sensitivity, specificity and positive and negative predictive values of a given diagnostic test (although these same principles may also be applied to aspects of history-taking or physical examination). Whatever the subject of investigation, an appropriate "gold standard" must always be chosen for comparison. In this connection, the sensitivity of the various patterns seen in ventilation/perfusion lung scans of patients with suspected pulmonary embolism has been demonstrated elegantly in a prospective study, using pulmonary angiography as the gold standard.[11]

3. Questions of *frequency* concern the likelihood of a clinical event occurring under a given set of circumstances, for example, the probability of a solitary pulmonary nodule in a 30 year old nonsmoking woman from Ontario being an histoplasmoma. In general, two measures of frequency are encountered: incidence and prevalence. *Incidence,* the rate of occurrence of new cases of a given clinical condition in a population over a specified time period, is measured longitudinally in a cohort study. *Prevalence,* the fraction of a group possessing a clinical outcome of a given point in time, is measured in a cross-sectional study and is a function of both incidence and duration of disease.

4. Studies of *risk* attempt to identify factors associated with an increased likelihood of disease, providing answers to such questions as, "which patients with haemoptysis and a normal chest x-ray are more likely to have bronchogenic carcinoma and, therefore, should undergo bronchoscopy?" Estimates of relative risk in such a situation are obtained by observing and comparing populations with respect to their exposure to putative risk factors and the subsequent incidence of disease. Unfortunately, since such studies are observational, rather than experimental, the gain in feasibility is offset by a loss in scientific rigour. Populations that differ in the risk factor under study are likely to differ in other respects as well, leading to selection bias. Dealing with such unwanted differences represents the major challenge to the investigator in this type of study.

5. While studies of risk attempt to predict the occurrence of disease from a given set of risk factors, studies of *prognosis* deal with predicting the future course and outcome of a disease following its onset. One might ask, for example, "are there factors that predict the occurrence of relapse of symptoms in an acutely ill asthmatic patient treated with initial success in the emergency room?"

The use of the cohort study design is common to studies of both risk and prognosis. A major distinction is that while risk factors are conditions that, when present in well persons, are associated with an increased probability of acquiring disease, prognostic factors are conditions that, when present in persons already known to have disease, are associated with the likelihood of a given outcome of that disease.[12] While risk factors generally predict low-probability events, prognostic factors predict relatively frequent events. As well, while studies of prognosis "count" a variety of events (death, disability, other complications), studies of risk attempt to predict the probability of just a single event (occurrence of disease). It is important to recall that because studies of prognosis are based on samples, they are susceptible to sampling bias: for example, asthma may seem to be a much more disabling and difficult to manage disease when viewed from the perspective of a chest clinic, than it would appear to be in a community wide study.

6. Studies of *therapy* attempt to demonstrate that a new treatment changes the future course of a disease, without introducing unwanted adverse effects. Recent developments in the management of asthma illustrate the multiplicity of sources from which new ideas about therapy arise.[13] Efforts in basic biomedical research aimed at determining the mechanisms of the disease at a cellular level have led to an enhanced understanding of the role of airway inflammation in the pathogenesis of bronchial hyperreactivity and asthma. This in turn has led most investigators and clinicians to shift therapeutic emphasis away from bronchodilators to inhaled corticosteroids.[14] Innovations in therapy may also arise from the serendipitous observations of clinicians. Recently, for example, it was observed that patients with asthma and rheumatoid arthritis experienced improvement in the former condition while on methotrexate therapy for the latter.[15] This led to a randomised clinical trial of methotrexate in "steroid-dependent" asthma which, although not conclusive, suggested a benefit from treatment.[16] Likewise, findings from observational epidemiologic studies may have therapeutic impact. It has been shown, for example, in a longitudinal cohort study of occupational asthma, that the duration of exposure to the responsible agent in the workplace following the onset of symptoms is a major determinant of the subsequent duration and severity of symptoms.[17] This obviously points to the need for early diagnosis and then removal of the subject from the workplace.

Whatever the source of an idea for a proposed therapy

and however sound it appears to be in theory, it should only be put into practice in the face of sound scientific proof of efficacy. The randomised, controlled clinical trial (RCT) has thus become the gold standard in studies of therapy, since it is the one method in clinical epidemiologic research that most closely approximates a scientific experiment. Even so it is fraught with methodological, practical, and ethical problems, and despite its inherent advantages over other methods of assessing the effects of treatment, in a survey of three leading medical journals *(NEJM, JAMA,* and *Lancet)* from 1966-76, it constituted only 16% of the published studies of therapy.[18] Chest physicians can take pride in the fact that the first clinical trial using a properly randomised control group was of streptomycin in the treatment of pulmonary tuberculosis in 1948.[19] However, it is only recently that a number of conventionally accepted treatments in chest disease such as the use of antibiotics[20] and aminophylline[21] in acute exacerbations of chronic airflow limitations have been called into question and studied by means of large scale RCTs. While there is little doubt that these well designed and executed RCTs are expensive, the use of therapies in the absence of scientifically sound proof that they in fact do more good than harm, may ultimately be more so.

7. Studies of disease *causation* are important to clinicians because of their impact on the approach to three clinical tasks: prevention, diagnosis, and treatment. In epidemiologic studies, "cause and effect" is just one of several possible explanations for the finding of an association between a given variable and outcome. Because such associations may also arise from bias, chance, or confounding, several criteria (first proposed by Sir Austin Bradford Hill) must be met in order to establish that a factor is truly causal.[22] First, a temporal relationship, with putative cause preceding effect must be demonstrated. Second, the association must be strong, as expressed by a large odds ratio or relative risk. Third, a dose-response relationship should exist. Fourth, the relationship should be consistent across several studies in a variety of settings. Fifth, the relationship should demonstrate reversibility upon manipulation of the variable of interest. Finally, the association should "make sense" and be compatible with the currently accepted biology of the disease. Because the lack of feasibility of experimental designs in epidemiologic studies of causation necessitates a reliance on observational techniques, all of these lines of evidence must lead to the same conclusion in order to establish with reasonable certainty that an association is due to cause-and-effect.

It is obvious from the foregoing that the clinical epidemiologist's scope of scientific inquiry is wide. In addition to enabling him to undertake his own research, his training in methodology also makes him a valuable resource to other would-be investigators in his institution, in areas of study design, sample size calculations, and statistical analysis.

CLINICAL EPIDEMIOLOGY AS A BASIC SCIENCE FOR CLINICAL PRACTICE

While not everyone has the time or commitment to produce his own clinical research, each of us, in order to practise rational, sensible, and modern medicine, is obliged to consume, on a regular basis, the research findings of others. Although commitment to clinical epidemiologic research requires a higher level of skill and training in study design, methodology, and data analysis, the fundamental principles involved in producing and consuming research are very similar. Each of us must maintain well-honed skills at appraising the quality of scientific evidence, and in this connection a background in clinical epidemiology provides a means to the end. We must be able to ask ourselves appropriate questions when reading the medical literature: is a study of a therapeutic intervention truly randomised, and if not, have the investigators tried to control for unwanted differences between comparison groups? Has a study of a new diagnostic test used a gold standard? Are there several lines of evidence for causation in a study describing a new association between variable X and disease Y? In our clinical practices, clinical epidemiology is not so much a separate discipline as an orientation or attitude. We must be able to support our clinical decisions with scientific evidence, and must be able, as best we can, to attach probabilities of outcomes to our diagnostic and therapeutic actions and our prognostications. No longer is it acceptable to resort to intuition and anecdotal experience and call it "clinical judgement".

CLINICAL EPIDEMIOLOGY AS A BASIC SCIENCE FOR CLINICAL TEACHING

Finally, clinical epidemiology may serve as a useful vehicle for our educational activities in the lecture theatre and at the bedside. Too often we take for granted our students' and houseofficers' understanding of the clinical decisions that we make day to day. Although having to explain what has become second nature to us may at times be tedious, it is often a useful exercise to dissect a decision and inspect its anatomy more closely. What we want trainees to remember is not so much the knee-jerk reaction of clinical situation X leading to decision Y, but the various elements that constitute that decision: the likely outcomes of various courses of action (preferably with probabilities), the accuracy of the results of a given diagnostic test and the influence those results are likely to have on subsequent decisions, the source and quality of scientific evidence supporting the choice of therapy A over therapy B. We need to foster an attitude of inquiry in students and residents and encourage them to challenge us.

No residency training program can ensure the exposure of each trainee to all types of clinical problems, whether in chest disease or, particularly, in as broad a discipline as internal medicine. All one can hope to accomplish is to enable trainees to gain some experience

in dealing with most of the common diseases with which they will be confronted in their subsequent careers, and to supervise and facilitate their acquisition of the necessary cognitive, technical and affective skills. It is also essential that residents be equipped with the skills or first principles necessary to deal with the new and unfamiliar clinical problems that they will undoubtedly encounter once they are in practice. These skills of course include the ability to establish a patient data base through proper techniques in history taking and physical examination, and the selection of appropriate diagnostic tests. Of equal importance, however, is the ability to use the medical literature to solve clinical problems: trainees must know, first, how to find the scientific articles they need; second, how to appraise critically the quality of the evidence with which they are presented; and third, how to integrate new information into their existing knowledge base. It is the responsibility of residency training programs to provide the opportunity to acquire these skills, and it is in this area that clinical epidemiology has a powerful role to play in postgraduate medical education.

However, we must use common sense and be aware of the demands on the housestaff's time in applying these principles. If we become mired in the "paralysis of analysis" of attempting critical appraisal of all clinical decisions, we will find students and houseofficers viewing clinical epidemiology with the same kind of disdain with which many of them have traditionally (and sophomorically) viewed classical epidemiology and public health. There are some clinical situations in which, for example, the value of a treatment is obvious from clinical experience alone: clearly, we do not have to waste time discussing the proof of efficacy of antibiotics in bacterial pneumonia, chest tube drainage in empyema, or oxygen therapy in acute respiratory failure. We can on the other hand, use our knowledge of epidemiologic principles to predict the most likely organism causing a pneumonia, and thereby choose our empiric antibiotic therapy more rationally. We must not forget that clinical epidemiology is after all a methodology, not a religion. If we use it judiciously in our pedagogical activities, I believe that we can make clinical medicine that much more interesting, exciting and understandable for students.

CONCLUSION — CLINICAL EPIDEMIOLOGY AND CLASSICAL EPIDEMIOLOGY

Fears that clinical epidemiology may eclipse so-called classical epidemiology are, I believe, unfounded, for there is a vital role to be played by both disciplines. Certainly in chest disease, there is a need for more classical epidemiological studies in occupational lung disease (identifying hazardous substances, determining frequency of disease states, and describing the natural history of occupationally related lung disease), and in the investigation of asthma mortality, among other pressing issues. I prefer to see clinical and classical epidemiology as two points on a continuum, with much overlap. Dr. Paul in a later paper said that ". . . the clinical epidemiologist is to the [classical] epidemiologist as the gardener is to the farmer".[23] I think this is an apt analogy; the farmer and gardener share common interests, use similar methodology, can work together harmoniously, but differ slightly in their orientation and devote varying portions of their time to their vocation or avocation, respectively. Moreover, both derive tremendous satisfaction from their work, particularly when it comes to fruition. □

References

1. MacMahon B, Pugh, TF. *Epidemiology: principles and methods.* Boston: Little, Brown and Company, 1970, p. 1.
2. Doll R, Hill AB. Smoking and carcinoma of the lung. Preliminary report. *Brit Med J* 1950; **2:** 739-748.
3. Doll R, Hill AB. The mortality of doctors in relation to their smoking habits. A preliminary report. *Brit Med J* 1954; **1:** 1451-1455.
4. Paul JR. President's address: clinical epidemiology. *J Clin Invest* 1938; **17:** 539-541.
5. Sackett DL. Clinical epidemiology. *Am J Epidemiol* 1969; **89:** 125-128.
6. Spitzer WO. Clinical epidemiology. *J Chron Dis* 1986; **39:** 411-415.
7. Sackett DL, Tugwell P, Haynes B. *Clinical epidemiology: a basic science for clinical medicine.* Boston/Toronto: Little, Brown and Company, 1985.
8. Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology: the essentials.* 2nd Edition. Baltimore: Williams and Wilkins, 1988, p. 2.
9. Fletcher and Fletcher, p. 37.
10. Nocturnal Oxygen Therapy Trial Group: Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. *Ann Intern Med* 1980; **93:** 391-398.
11. Hull R, Hirsh J, Carter C, *et al.* Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med* 1983; **98:** 891-899.
12. Fletcher and Fletcher, pp. 106-107.
13. Fletcher and Fletcher, p. 129.
14. Clark TJH. Inhaled corticosteroid therapy: a substitute for theophylline as well as prednisolone? *J Allergy Clin Immunol* 1985; **76:** 330-334.
15. Mullarkey MF, Webb R, Pardee NE. Methotrexate in the treatment of steroid-dependent asthma. *Ann Allergy* 1986; **56:** 347-350.
16. Mullarkey MF, *et al.* Methotrexate in the treatment of corticosteroid-dependent asthma: a double-blind crossover trial. *N Eng J Med* 1988; **318:** 603-607.
17. Chan-Yeung M, Lam S, Koerner S. Clinical features and natural history of occupational asthma due to western red cedar *(Thuja plicata). J Allergy Clin Immunol* 1987; **79:** 792-796.
18. Fletcher RH, Fletcher SW, Greganti MA. In: Roberts EB, Levy RI, Finkelstein SN, Moskowitz J, Sondik EJ, (ed). *Biomedical Innovations.* Cambridge, MA: MIT Press, 1981.
19. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *Br Med J* 1948; **2:** 769-782.
20. Anthonisen NR, Manfreda J, Warren CPW, *et al.* Antibiotic therapy in exacerbations of chronic obstructive lung disease. Ann Intern Med 1987; **106:** 196-204.
21. Rice KL, Leatherman JW, Duane PG, *et al.* Aminophylline for acute exacerbations of chronic obstructive pulmonary disease: a controlled trial. *Ann Intern Med* 1987; **107:** 305-309.
22. Fletcher and Fletcher, pp. 216-220.
23. Paul JR. *Clinical epidemiology.* Revised Edition. Chicago/London: University of Chicago Press, 1966, pp. 10-11.

Gestational Trophoblastic Disease Registry
UPDATE 1988

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A total of 37 new patients were entered into the Nova Scotia Gestational Trophoblastic Disease Registry and Surveillance Program in 1988. Nineteen patients were confirmed to have benign hydatidiform mole (HCG titres return to normal with no treatment other than the original D&C); four patients developed NMGTD; fourteen patients had partial (incomplete) mole. (Table I)

TABLE I

1. **Benign GTN**
   A. Hydatidiform Mole
2. **Malignant GTN**
   A. Non-metastatic (NMGTD)
      1. Persistent Hydatidiform Mole
      2. Invasive mole
      3. Choriocarcinoma
   B. Metastatic GTN (MGTD)
      1. Good prognosis, low risk
      2. Poor prognosis, high risk
         a) Initial urinary HCG titre > 100,100 IU/24 hr. or serum HCG titre > 40,000 mIU/ml
         b) Duration of symptoms > 4 months
         c) Liver or brain metastasis
         d) Previous chemotherapy
         e) Disease following term pregnancy

GLOSSARY:

HCG — Human Chorionic Gonadotrophin (Amerlex-M serum Beta sub unit assay)

NMGTD — Non-metastatic gestational trophoblastic disease

MGTD — Metastatic gestational trophoblastic disease

PRESENTATION

Ultrasound plays a major part in the diagnosis of the hydatidiform mole. Of the 23 patients referred to the registry (including benign and non-metastatic disease) all had ultrasound determinations performed, and 20 ultrasounds were positive for hydatidiform mole. The 3 patients who had negative ultrasound examinations were subsequently found to have a molar pregnancy. This represents a false negative rate of 13% for ultrasonography. Three patients were diagnosed following uterine curettage for the following: incomplete abortion(1), missed abortion(2).

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Benign Hydatidiform Mole

Of the 19 patients confirmed to have hydatidiform mole, 13 patients had titres return to normal in 6-8 weeks. HCG titres in four patients returned to normal in 10-12 weeks. Two patients had titres which took 20 and 21 weeks before gradually returning to normal.

Eight patients were referred to the registry by pathologists and the remaining eleven patients were referred by gynaecologists.

The median age of these 19 patients was 24.9 years — the youngest age 17 and the oldest age 36. The primary presenting symptom was abnormal vaginal bleeding which occurred in 16 patients. Five patients were noted to have a uterus large for their due dates in our report, while two patients had a uterus smaller than the normal.

Malignant Gestational Trophoblastic Disease

A. Nonmetastatic (NMGTD)

1) *Persistent hydatidiform mole*
Four patients developed nonmetastatic gestational trophoblastic and required adjunctive chemotherapy to eradicate their disease.

All four patients had HCG titres which initially began to fall. After 3-5 weeks the HCG titre began to rise. All four patients were treated with 2 courses of the Methotrexate® with Leucovorin® regimen. HCG titres returned to normal (three consecutive negative titres) 4-5 weeks following the second course of treatment. Follow up to date has been uneventful.

2) *Invasive mole*
No cases of invasive mole registered in the 1988 year.

3) *Choriocarcinoma*
No cases of choriocarcinoma registered in the 1988 year.

B. Metastatic gestational trophoblastic disease

1. or 2. No registered cases in the 1988 year.

FOLLOW-UP CASE STUDY

The following case study is presented for your information. This 24 year old gravida 1, para 0 patient was admitted to hospital with symptoms of vaginal bleeding and cramping. An ultrasound showed one normal fetus, approximately 13 weeks gestation and one molar pregnancy, thought to be fraternal twins. The bleeding and cramping subsided after 24 hours and it was elected to observe the patient closely at this point. Five weeks later the patient spontaneously delivered a 22 week fetus, which lived an hour and a half. A D&C was done for manual removal of the placenta and retained molar tissue.

On review of the slides by our registry pathologist, the comment was that the presence in the first specimen of a few chorionic villi which are dilated and show mild trophoblastic proliferation with evidence of edema and avascularity, raises the question of possible hydatidiform mole. Subsequent specimens showed no evidence of residual trophoblastic disease. HCG titres dropped and at the 11 week mark three consecutive negative titres had been obtained. Follow up has been uneventful to date.

TABLE II

EXPERIENCE OF THE TROPHOBLASTIC DISEASE REGISTRY IN 1988

1.	**Benign GTD**	
	A. Hydatidiform mole	19
II.	**Milignant GTD**	
	A. Nonmetastatic (NMGTD)	
	1. Persistent hydatidiform mole	4
	2. Invasive mole	0
	3. Choriocarcinoma	0
	B. Metastatic GTD (MGTD)	0
	Partial mole	14
	TOTAL	**37**

TOTAL EXPERIENCE — GESTATIONAL TROPHOBLASTIC DISEASE REGISTRY

A total of 440 patients (partial mole excluded) have been registered by the Nova Scotia Gestational Trophoblastic Disease Registry as of December, 1988. (Table III)

TABLE III

TOTAL EXPERIENCE (Excludes Partial Mole)

	1965-75	1976-80	1981-85	1986	1987	1988
Nova Scotia	40(12)	108(13)	72(14)	18(1)	12(1)	11(2)
New Brunswick	8(6)	31(2)	46(8)	5(3)	3	8(2)
Prince Edward Island		4(0)	9(0)	0	2	2
Newfoundland		15(4)	39(5)	2(2)	1	2
St. Pierre		1(0)				

Total number of patients — 440
Total requiring Rx (in parenthesis) 70 or 17%

Benign Gestational Trophoblastic Disease

Hydatidiform Mole

Three hundred and sixty-four patients were confirmed to have benign hydatidiform mole requiring no treatment other than the original D&C. (Table IV)

TABLE IV

1.	**Benign GTD**	
	A. Hydatidiform mole	364
II.	**Malignant GTD**	
	A. Nonmetastatic (NMGTD)	
	1. Persistent hydatidiform mole	54
	2. Invasive Mole	0
	3. Choriocarcinoma	3
	B. Metastatic GTD (MGTD)	17
	Non gestational choriocarcinoma	1
	Placental site trophoblastic lesion	1
		440

Malignant Gestational Trophoblastic Disease

Nonmetastatic

Fifty-four patients developed persistent nonmetastatic gestational trophoblastic disease. Three of these patients developed histologically confirmed choriocarcinoma. (Table V) All 54 patients remain alive and well.

Metastatic Gestational Trophoblastic Disease

Seventeen patients developed persistent metastatic disease. Six of these had histologically confirmed choriocarcinoma. (Table V) Four of the patients with metastatic choriocarcinoma died. Three were diagnosed following a normal pregnancy and died either of advanced disease or complications of chemotherapy. The fourth patient, who presented with choriocarcinoma etiology unknown, had a 2½ year remission between the time of her original treatment and recurrence. She was treated extensively with chemotherapy but expired in 1987.

The remaining 13 patients with MGTD remain alive and well.

TABLE V

CHORIOCARCINOMA (confirmed histologically)

	Metastatic	Nonmetastatic
Post Ectopic	1	
Post molar pregnancy		1
Post normal pregnancy	4 (3 died)	1
Etiology unknown*	1	
Post hysterectomy — DUB**		1

*recurrent choriocarcinoma - expired 1987
**positive pregnancy test

Five patients remain alive and well.

Non-gestational choriocarcinoma

One patient presented with non-gestational choriocarcinoma. This patient's case history was published in the 1987 registry report. Her titres remain normal with 17 months left in a 24 monthly follow-up program.

THE INCOMPLETE OR PARTIAL MOLE

In 1981, a study to evaluate the clinical significance of the partial mole (hydatidiform degeneration) was begun.

To date 54 patients with partial mole have been followed by the registry. Dr. I. Zayid of the Dr. D. J. MacKenzie Diagnostic Center has reviewed the pathology on 52 of these patients. Two patients were lost to follow up.

Of these patients, 41 had HCG titres which returned to normal in eight weeks or less, 9 patients entered the study late (8 at 11 weeks, 1 at 22 weeks) and their titres were normal at entry. Two patients had titres which took 12 and 13 weeks prior to returning to normal.

Follow up for the 52 patients has been uneventful and ranged from five to twelve months (forty-nine patients) one to two months (three patients).

In 1988, 14 patients were diagnosed with partial (incomplete) mole.

Nine of these patients had titres return to normal in 4-8 weeks; two patients had titres which took 12 and 13 weeks before returning to normal; three patients entered the study late at 11 and 12 weeks with normal titres.

These 14 patients had a median age 27.3 years, the youngest age 16 and the oldest age 41. Eight patients were referred to the registry by pathologists, referred by gynaecologists and one patient was picked up on review of titres by the registry co-ordinator.

Ten of the 14 patients followed in 1988 experienced vaginal bleeding, three complained of abdominal pain, one with low back pain. The size of the uterus was smaller than dates in three patients. Larger than dates in one patient. Uterine size was appropriate for dates in the remaining 10 patients. Two patients had no symptoms and the partial mole was picked up following a therapeutic abortion.

The registry will continue to recommend 6 months of follow up with HCG titres for the patient with partial mole. This decision is based on recent literature which suggests that 5-9% of patients with partial mole will develop persistent gestational trophoblastic disease. (Natural History of the Partial Molar Pregnancy, *Obst Gynaecol* 1985; Vol. 66).

FOLLOW-UP RECOMMENDATIONS

Between 15-20% of the patients who have had a molar pregnancy will require adjunctive chemotherapy or an occasional patient will require surgery to eradicate their disease. For this reason, follow-up with HCG titres is *essential.* Registration with the Trophoblastic Disease Registry is recommended for all cases and can be made by writing to:

Nova Scotia Gestational Trophoblastic
Disease Registry,
Room 5054, Ambulatory Care Center,
Victoria General Hospital,
Halifax, N.S. B3H 2Y9
or by phone (902) 428-2263
or fax (902) 428-3765

The follow up protocol for patients with gestational trophoblastic disease as recommended by the Nova Scotia Gestational Trophoblastic Disease Registry is as follows:

After hospital discharge

a) HCG weekly until three consecutive normal values are achieved. Then . . .
b) HCG monthly for one year. Pregnancy is permissable after 6 months of normal titres. If pregnancy is suspected an ultrasound is indicated for early confirmation.

If chemotherapy was required for low risk trophoblastic disease follow-up is as follows:

a) HCG weekly until three consecutive normal values are obtained. Then . . .
b) HCG monthly for one year. Then . . .
c) HCG once every three months for one year. Pregnancy is permissable after one year of normal titres. If pregnancy is suspected an ultrasound is indicated for early confirmation.

If chemotherapy was administered for high risk trophoblastic disease follow-up is as follows:

a) HCG weekly until three consecutive normal values are obtained. Then . . .
b) HCG once a month for two years. Pregnancy is permissable after two years of normal titres. Once again, if pregnancy is suspected an ultrasound is indicated.
c) HCG once every three months for the third year.
d) HCG titres once every six months for the fourth year.
e) Yearly thereafter. □

ACKNOWLEDGEMENT

Best wishes and thank you to Dr. R. C. Fraser who has been the director of the registry since 1975. Before 1975, Dr. Fraser followed trophoblastic disease patients on his own and later was instrumental in the formation of the registry. Without ever having seen Dr. Fraser, many patients owe him deep gratitude for their good health today. Dr. Fraser is presently the Head of the Department of Gynaecology at the Victoria General Hospital.

Our sincere thanks for the continued support of the patients, physicians and pathologists.

Colonic Angiodysplasia

Catherine M. Coady,* BSc, MD and M. T. Casey,** BSc, MD CM, FRCS(C), FACS

Halifax, N.S.

Identifying the source of lower gastrointestinal bleeding often poses a challenge to the investigating physician. Technological advances such as selective angiography and radionuclide scanning have greatly enhanced the physician's ability to recognize that colonic angiodysplasia is an important cause of lower gastrointestinal bleeding of the elderly. The treatment approach obviously varies with the nature of bleeding, the distribution and numbers of vascular ectasias as well as on the general health of the patient. Treatment modalities may include endoscopic laser photocoagulation, vasopressin infusion, embolization or surgical approaches such as right hemicolectomy, subtotal colectomy and rarely total colectomy.

With the introduction of selective angiography in 1965, colonic angiodysplasia has been increasingly recognized as a common source of recurrent lower gastrointestinal bleeding, especially in the elderly population. Previously, unexplained vigorous lower G.I. bleeding was usually attributed to diverticular disease.

Angiodysplastic lesions are tiny collections of irregularly dilated, tortuous, thin-walled vessels, usually found in the submucosal layer of the colon. The patient's presenting symptoms are quite variable as the bleeding from these complex lesions ranges from being slow and steady to intermittent or even massive. There is a variety of terms used interchangeably with angiodysplasia such as vascular ectasia, vascular dysplasia, colonic ectasia or arteriovenous malformations.

INCIDENCE

The ectasias are typically observed in patients over the age of 65[1,2,3] and males and females are almost equally affected.[1] Associated medical conditions such as atherosclerosis, renal disease, diverticulosis, bleeding disorders and commonly, aortic stenosis have been reported.[1,3] The association between angiodysplasia and aortic stenosis has been questioned by Mehta *et al.*[4] and Imperiale and Ransohoff.[5] Mehta found that none of the patients in their study who were felt clinically to have aortic stenosis had any evidence of the disease as assessed by Doppler echocardiography.[4] Imperiale and Ransohoff in their review state that there were major methodologic deficiencies in the studies reporting the association between aortic stenosis and angiodysplasia.[5] Both groups suggest further controlled evaluation of this subject.

ETIOLOGY

There are several hypotheses regarding the etiology of angiodysplastic lesions. Many favour the theory that it is an acquired condition on the basis that the lesions tend to occur in older patients and that they may be multiple.[1] Boley *et al.* suggest that these vascular ectasias are due to the degeneration and progressive dilatation of previously normal vessel walls.[1] He postulates that the ectasias are the result of increased intraluminal pressure, which in turn causes venous congestion and obstruction of the submucosal veins as they penetrate through the muscular layer of the gastrointestinal wall. With continued venous congestion and obstruction, there is progressive dilatation of venules, capillaries, and arterioles eventually leading to arteriovenous communications. (Fig. 1)

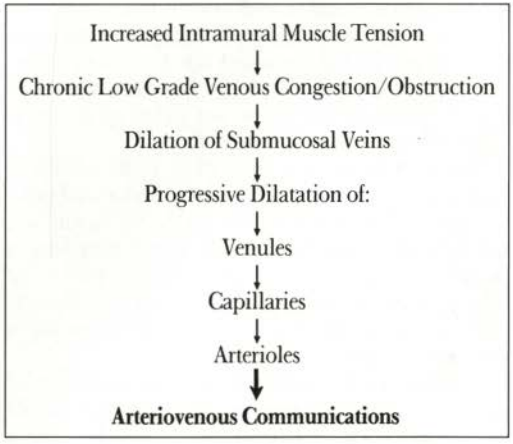

Fig. 1 Proposed etiology of angiodysplasia

PATHOLOGY

Angiodysplastic lesions appear as ectasias or dilatations of submucosal vessels. Their thin walls make them prone to erode or rupture which results in bleeding into the bowel lumen. Owing to their minute size, often measuring no more than 5 mm (range 1mm to 1cm), these lesions seldom produce gross abnormalities that are visible or palpable at surgery.[1,6] The lesions may be visualized when a resected portion of colon containing the ectasias is injected with silicone rubber intra-

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**Associate Professor, Department of Surgery, Dalhousie University, N.S.

arterially. This technique demonstrates their characteristic "coral reef" appearance.

Boley *et al.* report localizing the ectasias in the cecum and proximal ascending colon only.[1] Their explanation for this phenomenon is that according to LaPlace's law, the intraluminal pressure and tension are greatest in the part of the bowel with the widest diameter. However, the ectasias have been found throughout the colon.[3] Indeed, these malformations have been observed in other areas of the G.I. tract such as the stomach[7] and small intestine.[8]

CLINICAL FEATURES

Patients with suspected angiodysplasia usually present with recurrent episodes of painless lower G.I. bleeding which may be bright red or maroon blood per rectum with or without clots.[6] Alternatively, they may present with melena or asymptomatically with iron deficiency anemia secondary to slow continuous bleeding from an ectasia.

Angiodysplasia must be differentiated from diverticulitis, another common cause of lower G.I. bleeding in elderly patients. Clinically, it is often difficult to distinguish between these two sources of bleeding. Individuals with diverticulitis usually have one brisk bleeding episode only versus patients with angiodysplasia who may have recurrent bleeding which is not necessarily brisk.[9] Other lesions that must be excluded as the cause of bleeding include hemorrhoids, cancer, ulcerative colitis, ulcers, polyps, and Crohn's which are typically identified in the diagnostic work-up.

DIAGNOSIS

The diagnosis of angiodysplasia often poses a challenge to the investigating physician as the initial work-up may fail to reveal the source of bleeding and/or perhaps the diagnosis has not been contemplated. Thus, many patients may go for quite some time without ever having a cause identified for their overt or occult gastrointestinal blood loss. Accordingly, the physician ought to have angiodysplasia high on the differential diagnosis list, especially when elderly patients present with recurrent lower G.I. bleeding, the source of which has not yet been found.

The investigative approach to a patient who presents with rectal bleeding, characteristic of angiodysplasia, is outlined in the algorithm in Fig. 2. The physical examination is often negative especially if the bleeding has ceased. Coagulopathies have been identified as being a significant risk factor in the diagnosis of angiodysplasia.[3] Thus, a coagualation panel including platelet function be assessed. A gastric aspirate should be done to rule out upper G.I. bleeding. Sigmoidoscopic examination is also typically negative although hemorrhoids may be found as an incidental finding. A barium enema is usually not indicated in the initial assessment of a patient suspected of having angiodysplasia, as it is often not helpful and will mask any features on angiogram. Emergency colonscopy is also of limited value, especially if there is massive bleeding because the field is obscured by blood. If the bleeding has arrested, colonoscopy may be valuable in revealing small areas of tortuous dilated submucosal vessels or small punctate lesions. At this point the colonoscopic treatment modalities such as laser photocoagulation may be initiated.[2]

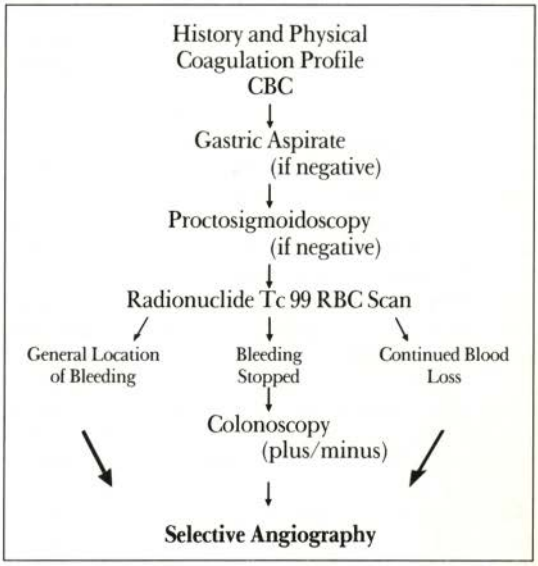

Fig. 2 Algorithm for diagnostic evaluation of patients with suspected angiodysplasia.

If colonoscopy has been unsuccessful, the next step is to proceed to selective angiography which has proved to be the gold standard in identifying angiodysplasia. The triple vessel approach is taken starting with the superior mesenteric then inferior mesenteric and finally celiac arteries. The following have been identified as characteristic radiographic features of angiodysplasia:[6]

1. dense, slowly emptying vein
2. vascular tuft
3. early filling vein
4. extravasation of contrast material

Diverticular bleeding is demonstrated as a pooling of blood within a specific diverticulum.

Also available recently are nuclear medicine techniques such as tagged Tc 99 red blood cell scans. These scans allow the identification of bleeding points due to hemorrhage of a lesser magnitude. Furthermore, they are less invasive than angiograms. However, the drawbacks are that they require active bleeding, and are rather nonspecific in terms of identifying the nature of the bleeding lesion. As radionuclide scans become more widely used, they can be done prior to angiography to localize and establish the presence of bleeding, as well as allow the rapid selection of the artery to be injected at angiography. Thus, angiography may eventually only be performed in patients with positive scans.

TREATMENT

Once the source of bleeding has been identified, appropriate management can be instituted. Depending on the nature, amount and distribution of the lesions and on the patient's status, a medical or surgical route may be taken.

The non-operative control of the hemorrhage may be achieved by embolization, infusion of vasopressin or laser photocoagulation via endoscopy.[2] These methods are preferred for individuals with multiple lesions, widely scattered lesions, upper G.I. lesions or if the patient is deemed unsuitable for surgery.

If these techniques are unsuccessful and/or if the lesions are localized to the cecum and ascending colon, a right hemicolectomy may be performed. This removes the bleeding angiodysplastic lesions as well as any satellite lesions which may be present. If a patient is found to have multiple lesions and bilateral colon involvement, a subtotal colectomy may be indicated.[3] However, there is a high morbidity associated with this operation in the elderly.

The picture is more complex if there is concomittant diverticular disease. If there are diverticula present in the left and right colon, Boley *et al.* advocate doing a right colectomy as 80% of bleeding diverticula are located in the right colon.[1] Furthermore, they contend that the risks of keeping the left colon are far outweighed by the increased morbidity and mortality of a subtotal colectomy particularly in elderly patients.[6]

In the event of an acute hemorrhage which has failed to stop and when no lesion has been defined via any of the available armamentarium, a subtotal or total colectomy is generally accepted by some as the route of choice.[1]

SUMMARY

Angiodysplasia is now being recognized as a common cause of gastrointestinal bleeding in elderly patients. Diagnosis remains a challenge but should be suspected in an elderly patient who presents with recurrent episodes of bleeding, especially if preliminary investigations have been negative. Angiography remains the gold standard in diagnosing these lesions. Methods of treatment include laser photocoagulation, vasopressin infusion, and surgical approaches. □

References

1. Boley SJ, Sammartano R, Brandt LJ, and Sprayregen, S. Vascular Ectasias of the Colon. *Surg Gynecol & Obst* 1979; **149:** 353-359.
2. Gostout CJ, Bowyer BA, Ahlquist DA, Viggiano TR, Balm RK. Mucosal Vascular Malformations of the Gastrointestinal Tract: Clinical Observations and Results of Endoscopic Neodymium: Yttrium-Aluminum-Garnet Laser Therapy. *Mayo Clin Proc* 1988; **63:** 993-1003.
3. Smith GF, Ellyson JH, Parks SN, Nichols JG, Peters RS, Williams J, Bezmalinovic Z, Peter ET. Angiodysplasia of the Colon. *Arch Surg* 1984; **119:** 532-535.
4. Mehta PM, Heinsimer JA, Bryg RJ, Jaszewski R, Wynne J. Reassessment of the Association between Gastrointestinal Arteriovenous Malformations and Aortic Stenosis. *Am J Med* 1989; **86:** 275-277.
5. Imperiale TF, Ransohoff DR. Aortic Stenosis, Idiopathic Gastrointestinal Bleeding, and Angiodysplasia: Is There an Association? *Gastroenterol* 1988; **95:** 1670-1676.
6. Boley SJ, DiBiase A, Brandt LJ, Sammartano RJ. Lower Intestinal Bleeding in the Elderly. *Am J Surg* 1979; **137:** 57-63.
7. Gunnlaugsson O. Angiodysplasia of the Stomach and Duodenum. *Gastrointestinal Endoscopy* 1985; **31:** 251-254.
8. Monk JE, Smith BA, O'Leary JP. Arteriovenous Malformations of the Small Intestine. *Southern Med J* 1989; **82:** 18-22.
9. Potter GD, Sellin JH. Lower Gastrointestinal Bleeding. *Gastrenterol Clin North America* 1988; **17:** 341-355.

Current Topics in Community Health

Selected by: Dr. Lynn McIntyre
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PICTOU PHYSICIANS FIGHT TOBACCO SALES IN PHARMACIES

The sale of tobacco products in pharmacies is unacceptable to the medical staff at the Sutherland Harris Memorial Hospital (SHMH) in Pictou, Nova Scotia. They have implemented a three-step strategy to pressure pharmacies to stop such sales. The first step was to convince the only pharmacy within the immediate catchment area of the hospital to discontinue its tobacco sales. The second step was for the medical staff to encourage patients to take their prescriptions to pharmacies which did not sell tobacco products. Thirdly, a policy was adopted by the physicians whereby they would not prescribe or re-order prescriptions by telephone to pharmacies which continued to sell tobacco products.

A letter outlining the policy was sent to all affected pharmacies in Pictou County. It was explained that doctors would continue to accept calls for urgent problems or to clarify prescriptions. Patients who patronized non-compliant pharmacies were also given a letter and the policy was explained to them during their next office visit. It was clearly indicated that they had the right to take their business where they chose, but if they wished to purchase their drugs at these stores, adequate written prescriptions would have to be obtained during regular office visits. This inconvenience was expected to lead patients to change their buying patterns and thereby encourage pharmacies to cease the sale of cigarettes and other tobacco products as a response to potential customer loss. To date, there has been quiet acceptance of this policy by patients and pharmacies.

Although to most physicians the hypocrisy of tobacco sales by pharmacies is obvious, to most pharmacies it is not. It is hoped that pharmacists and pharmacy managers who are unwilling to respond to moral suasion may respond to financial pressure. In Pictou, unanimous support by members of the medical staff and the availability of smoke-free pharmacy options facilitated the introduction of this tactic. It could, however, be readily adopted by group or solo physicians in other areas.

Submitted by: Dr. Gordon V. Young, Medical Staff, Sutherland Harris Memorial Hospital

Comment

The letter to patients of the Medical Staff of SHMH states that:

"Tobacco products constitute the largest preventable cause of sickness and death in our society. The medical staff of the SHMH is actively trying to discourage their use in our community. We feel that members of the health care team should be doing everything possible to discourage the consumption of tobacco products. A glaring inconsistency is the sale of these products by pharmacies.

Our medical staff has unanimously adopted a policy to discourage the people under our care from taking their prescriptions to pharmacies which sell tobacco products. As well, we have adopted a resolution not to phone prescriptions or re-order prescriptions by telephone to pharmacies which sell these items.

We recognize that patients have the right to deal with the drug store of their choice and if you choose to deal with a pharmacy that sells these products, that you receive written prescriptions during your regular office visits. That pharmacies in Pictou County which do not carry tobacco products are Dodson's Pharmacy in Pictou, Fulton's Pharmacy in River John, MacLeod's Pharmacy in New Glasgow, and Pictou Pharmacy in Pictou.

Your cooperation in this matter is greatly appreciated.
Signed: All 8 physicians on medical staff SHMH"

Physicians across Nova Scotia are urged to consider the Pictou physicians' tobacco control strategy in their own communities.

NATIONAL SURVEY ON DRINKING AND DRIVING

The National Survey on Drinking and Driving was a random digit-dialing telephone survey undertaken by the Health Promotion Directorate of Health and Welfare Canada in March 1988. Over 10,000 Canadians, ages 16-69, residing in the Canadian provinces were included.

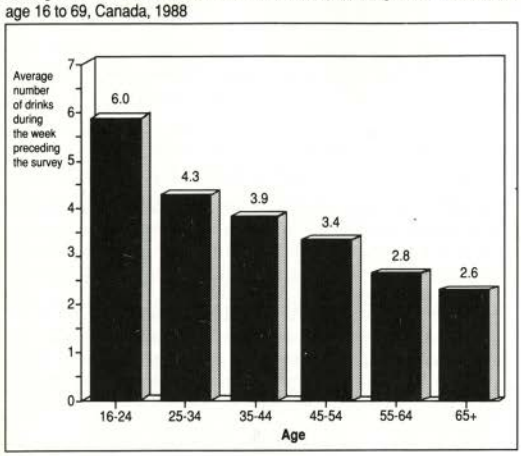
Who Drives?

The vast majority (85%) of Canadians aged 16-69 years are drivers. More men than women drive — 93% compared with 78%. University-educated Canadians and those with higher incomes are more likely to drive than are those with elementary education or lower income groups (93% of high income Canadians drive compared to 67% of low income persons).

Who Drinks?

Nearly 8 out of 10 Canadians said that they had had a drink in the last 12 months. Men are more likely than women to report that they drink — 83% compared with 75%. Higher rates of alcohol consumption are reported by university-educated people (89%) than by those with an elementary education (54%). Single persons (83%) are more likely to drink than those of any other marital status, and younger Canadians imbibe more than their older counterparts.

Average number of drinks consumed in the week preceding the survey, by age, age 16 to 69, Canada, 1988



The average number of drinks consumed in the week preceding the survey for both sexes was sharply higher for younger people than for older persons (Fig. 1). By far the most popular place to drink is the home — 62% reported doing so during the past week, compared to the next most popular location — a bar, tavern or pub (31%). A considerable proportion of people also reported drinking in restaurants (23%), at other people's houses (22%) and at other social events such as weddings (15%) over the previous week. These locations may prompt some drinkers to also drive home.

Who Drives After Drinking?

The survey showed that in the past year, 17% of Canadians in the target age group drove after having had two or more drinks in the preceding hour. This figure represents 24% of those who said that they were both drivers and drinkers. Men are three times more likely than women to report driving after drinking (26% compared with 8%). They also do it more often — 17% of men reported having driven after drinking on three or more occasions in the past month, compared with 9% of women. Other groups where about one-quarter of people surveyed reported driving after drinking in the past year included those under age 34, single people, and those in higher income brackets.

The most "at risk" Canadians were young men aged 16-24, 41% of whom reported driving after drinking in the past year. This finding is particularly relevant in light of the high motor vehicle accident mortality rate of this age group, most of which is attributable to impaired driving.

Why do People Have to Drive after Drinking?

About one-quarter of those who reported drinking and driving said that they *had* to do so in the past year. These individuals were younger and better educated than those who did not. Not wanting to leave the car (40%), a lack of public transportation (27%), a lack of desirable alternatives (24%), and feeling responsible for getting other people home (14%) were the reasons given to explain why people had to drive while impaired. • Only 2% attributed their action to an unexpected emergency.

Why do People Ride with Impaired Drivers?

In the 12 months preceding the survey, 27% of Canadians said they had been a passenger with a driver they believed had had too much to drink; of those, only 64% said they were concerned for their safety. Canadians who have ridden with an impaired driver are likely to be impaired themselves (42% compared with 19% of those who have not); they are usually friends (67%); and they are usually younger (44% of those aged 16-24 compared with 20% of those aged 35-44 years).

The most popular reason for riding with an impaired driver is that no alternative transportation was available, an answer given by 46% of Canadians (51% of women and 42% of men). Other reasons included not wanting to leave the driver or wanting to keep the driver alert (11%) and not having far to go (8%).

Avoiding Drinking and Driving

Thirty-eight percent of Canadians aged 16-69 claimed to have acted to avoid drinking and driving over the past year. The tactic most often used among these people was to stop drinking early or to wait at least one hour before driving. Asking someone else to drive (60%), walking or taking a taxi, bus or subway (44%), and staying overnight (38%) were the next most used approaches.

In all age groups (49%) and for both sexes (54% of women, 45% of men), the fear of having an accident was the most frequently reported deterrent. Another 37% said they were afraid of getting caught by the police, while 18% were afraid of losing their driver's licence or of being jailed. Over one-third of Canadians (39%) felt it was wrong to drink and drive.

Only 6% of Canadians acknowledged that someone had tried to stop them from driving after drinking; surprisingly, 40% said they had tried to stop someone else from doing the same over the past year. The most successful tactic to prevent someone from driving after drinking is to ask the person to stay over — 85% of people who reported this strategy were successful. Offering someone a ride home meets with success 84% of the time. Also effective are taking away the person's car keys (78%), and suggesting an alternative form of transportation (72%).

Source: Health and Welfare Canada. National Survey on Drinking and Driving 1988, Overview Report, Minister of Supply and Services Canada, 1989

Continued on page 125

Personal Interest Notes

Dr. H. C. (Curly) Still was presented with the 1990 Family Physician of the Year Award in St. John's, Newfoundland on July 22, 1990. This award is presented to one physician a year, and in this case, for "not only his outstanding compassionate competence as a physician and teacher, but for his own brand of cheerful courage." Congratulations from The Medical Society of Nova Scotia for this well deserved honour. (Dr. Still is a former Editor of *The Nova Scotia Medical Journal* many years ago.)

Dr. Emerson Moffitt, Anaesthetist and former Associate Dean of Dalhousie Medical School, has been awarded the Canadian Anaesthetists' Society Gold Medal at the Society's Annual meeting in Vancouver recently for outstanding achievement. Dr. Moffitt is now Professor of Anaesthesia and Editor of the Medical School Alumni magazine MeDAL. □

137th Annual Meeting

The Medical Society of Nova Scotia

This year's Annual Meeting will be launched at the official opening of the Society's New Headquarters, 5 Spectacle Lake Drive, City of Lakes Business Park in Dartmouth, on Thursday evening November 15th.

The Annual Meeting and Council Meetings as well as the Banquet and Ball will take place at the Nova Scotian Hilton Hotel International in Halifax.

REMEMBER THE DATES

NOVEMBER 15-17, 1990

Commenting on the interpretation of medical research studies, an editorial writer in New Scientist *for April 15, 1989 wrote: "The biggest dilemma is how to assess the validity of a study: publication is no guarantee that the research is sound and the conclusions warranted".*

NEONATAL ADVANCED LIFE SUPPORT INSTRUCTOR CERTIFICATION (NALS)

The Reproductive Care Program of Nova Scotia and the Nova Scotia Heart and Stroke Foundation are sponsoring a Neonatal Resuscitation (NALS) **Instructor** Certification.Workshop. Two representatives from each of the regional and tertiary institutions in Nova Scotia, as well as from the tertiary centers in New Brunswick and Prince Edward Island have been invited to attend. This two day workshop will prepare these representatives to become certified **instructors** in Neonatal Resuscitation. The Workshop will be held on October 23 & 24, 1990 at the Halifax Hilton Hotel. The Nova Scotia Heart and Stroke Foundation has generously provided the funding for a major portion of the Workshop, speakers and teaching supplies for each of the Nova Scotia centers.

The Canadian Heart and Stroke Foundation and the Canadian Paediatric Society have endorsed this program to be implemented across Canada and the goal is to have this program available to all perinatal staff in all hospitals regardless of size or geographic location. The team approach; ie: physician and nurse is the format used for this course. Upon completion of this Workshop the Nova Scotia participants will be expected to develop an in-house program to conduct provider courses that will certify all perinatal staff (both physicians and nurses) in their respective provincial regions in Neonatal Resuscitation. Hospitals need to ensure that staff have the appropriate neonatal resuscitation skills. It is vital to have someone present at every delivery who is skilled in neonatal resuscitation and to have additional skilled staff readily available to assist.

THE MEDICAL SOCIETY OF NOVA SCOTIA

NOVA SCOTIA DIVISION OF THE CANADIAN MEDICAL ASSOCIATION

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