sion of T-cells to less than 10% of normal was possible while the ALG was being administered and the T-cells returned to normal within 7 days, but that monitoring the suppression of specific antidonor cell-mediated lympholysis guided the clinical administration of ALG. In the study of Cosimi and colleagues[13] the cumulative incidence of rejections by day 21 was 25% in the treated group, compared with 60% in the control group, but increased to 60% in the treated group within 1 week of discontinuing ATG. The Canadian study, therefore, might have been more successful had ALG been given for a longer period of time and the immunosuppression of the patient monitored to ascertain when "breakthrough" occurred.[15]

P.S. Russell, a past president of the Transplantation Society, in his address to the society in August 1976 stated that the use of ALG and immunologic monitoring of the transplant recipient were two areas that afford "opportunities for the improvement of our clinical results in the near future.[16,17] It is important to recognize that, although there appears to be adequate data to conclude that ALG is clinically efficacious, this conclusion applies only to those ALG preparations that have proven to be so. With a costly agent such as ALG (the commercial preparation in Canada costing nearly $4000 per patient) and the lack of in vitro tests to predict clinically useful preparations, it is imperative that the clinician demand proof that the preparation being prescribed is indeed clinically immunosuppressive. Companies marketing ALG must demonstrate the clinical efficacy in man of the specific preparation, centres should administer the preparation for a minimum of 1 to 3 months, and the immune response of the recipient should be monitored so that the dosage and time of administration can be tailored to the patient's needs.

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The 1975 Declaration of Helsinki and consent

Just over a year ago the Declaration of Helsinki, adopted by the 18th World Medical Assembly in 1964, was revised when the 29th assembly met in Tokyo. The original declaration and the revision differ substantially. The differences reflect recent changes in both medical practice and social attitudes. The 1975 declaration also has implications for physicians whether they be therapeutic practitioners, basic science or clinical investigators, authors or editors. These differences and implications merit comment.

The Declaration of Helsinki was drafted as a guide to ethics for physicians engaged in clinical research. Clinical research, however, is not confined to laboratory investigation or controlled clinical trials, for to some degree every therapeutic procedure, however simple, is an individualized experiment — and for this reason the declaration should interest all physicians. In fact the 1975 declaration does have much wider impact than would have a document concerned purely with clinical research. One sentence in the 1975 declaration illustrates this wider impact: "In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards" (Introduction, paragraph 4). The 1975 declaration, then, is a summary of ethical principles relevant to all physicians.

The chief differences between the 1964 and 1975 declarations are the following, in addition to the sentence already quoted:

1. The purpose of biomedical research is included in the introduction; it is "to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathology of disease" (paragraph 3).

2. The distinction between research that is "essentially therapeutic" and research that is "purely scientific and without therapeutic value to the person subjected to the research" (1964 document) is retained but the word "direct" has been inserted before the words "therapeutic value" (Introduction, paragraph 6).

3. As a reflection of the concern for the environment initiated in the 1960s, the 1975 declaration recognizes that "special caution must be exercised in the conduct of research which may affect the environment" (Introduction, paragraph 7). This passage is followed by the humane words, "and the welfare of animals used for research must be respected".

4. The section detailing basic principles has been radically revised. The number of principles has increased from 5 to 12. There is now greater emphasis on the adequacy of research design; the need is recognized for a researcher to describe the design and conduct of experimental procedures involving human subjects to an independent protocol review committee, "for consideration, comment and guidance"; a greater degree of responsibility is placed on the supervision of research in regard to risk–benefit ratios and the rights and integrity of the research subject; and, in particular, the requirement is emphasized that "each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail", as is the freedom the subject has to withdraw from participation in a study when he or she desires. In addition two new principles are added:

- "The research protocol should al-

ways contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with" (Basic Principles, paragraph 12).

- "In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication" (Basic Principles, paragraph 8).

5. Much of the section dealing with clinical research and professional care has been rewritten. "The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods" (paragraph 2). Similarly, "In any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method" (paragraph 3). Also stressed are the need for the physician not to let a patient's refusal to participate in a study interfere with a physician–patient relationship, and the desirability of stating in the protocol the reasons a physician considers it essential not to obtain informed consent.

6. The final section of the 1964 declaration, covering nontherapeutic clinical research, is simplified. The main items concern the type of subject, the precedence of a subject's well-being over the interests of science and society, and the need to discontinue research if its continuation is thought to be harmful to the subject.

The 1975 declaration emphasizes the rights of the individual patient or subject. This aspect of the declaration is in many ways the most important; all physicians must give increasing attention to the matter of consent. The nature of consent and of the manner in which it is obtained and stated will vary according to circumstances of investigation, place and time, but any consideration of consent must, as a minimum, make provision for the following: (a) acknowledgement by the subject that a physician or researcher has fully explained the nature of the procedures to be followed and that the subject fully understands it; (b) acknowledgement by the subject that a physician or researcher has fully explained the risks entailed by a particular procedure and that the subject understands them and the possibility that unpredictable incidents may ensue; (c) agreement that the subject will submit to various specified procedures; and (d) recognition by the subject that withdrawal from the study is permissible at any point. These provisions are minimal requirements; the wise course for a physician to take is to consult the local medical school, university or hospital and to seek guidance regarding finer points from a review or ethics committee.

The Canadian Medical Association has made two points regarding consent. First, transmittal of the details of a proposed procedure to an independent protocol review committee "for consideration, comment and guidance" is less desirable than transmittal for definite action by a committee; that is, a committee should be empowered to accept or reject a study, depending on the ethical issues, rather than just consider and comment on the proposed study. Second, there is apparent contradiction between basic principle 9 ("each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study . . . The doctor should then obtain the subject's freely-given informed consent") and paragraph 5 of the section concerned with medical research combined with professional care ("If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol"). Admittedly the declaration has been prepared as a "guide", yet, as the document itself advises, the recommendations "should be kept under review in the future" — an indication that the declaration will need to be revised from time to time.

Consent concerns more than the researcher–subject relationship: a responsibility is now placed on both authors and journal editors to conduct their activities in an ethical manner. The physician–author is advised that he or she "is obliged to preserve the accuracy of the results" — advice that implies that scientific research is not always free of fraud. The journal editor is reminded that "reports of experimentation not in accordance with the principles laid down in this declaration should not be accepted for publication — advice based on the view that adherence to high standards of publication would make it clear to authors that manuscripts dealing with improperly designed studies would not be published, which would in the long run discourage unethical studies.

The 1975 declaration thus has shaped a new aspect to the author–editor relationship. If the traditional relationship between physician and patient is a "therapeutic alliance" and that between experimenter and subject a "scientific alliance",[1] the relationship between author and editor can be regarded as a communication alliance. The Journal will continue to respect the privilege of relationships between authors and itself, but the 1975 declaration, in conjunction with seminal statements by journal editors,[2,3] has increasing relevance to this aspect of medicine. For this reason it is hoped that authors will familiarize themselves with the Declaration of Helsinki of 1975 so that the communication alliance greatly respected by the Journal will continue to preserve the ethical standards that are directed ultimately to a single objective: the enhancement of medical standards and practice in Canada.

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