Progress

Newsletter of the Special Programme of Research, Development and Research Training in Human Reproduction

No. 8 1988

Chinese study confirms long-term safety of vasectomy

According to a recently published analysis of a WHO-supported study (TANG GUANG-HUA, et al. (1988) *International journal of epidemiology*, **17**(3): 608-616) conducted in the Sichuan province of China during 1983 to 1984, vasectomy is not associated with any long-term adverse health effects. In fact, vasectomized Chinese men appear to be healthier than those not vasectomized. The health indicators included in the study were mainly those for detecting cardiovascular disease, but the subjects participating in the study were also tested for other conditions, including rheumatism, asthma, and diabetes. The findings of this study are in agreement with a number of previous epidemiological studies, which too failed to find any association between a wide range of diseases and vasectomy. Such investigations have been conducted mainly in Europe, India and the USA.

Vasectomy as a method of family planning gained acceptance in the 1970s. Today it is estimated that there are some 50 million vasectomized men throughout the world. In spite of its increasing popularity and the fact that vasectomy is among the safest of all surgical procedures, there have remained some concerns about its possible long-term effects.

First, it had been shown in several studies that vasectomy increases antisperm antibodies

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About the Special Programme

The Special Programme of Research, Development and Research Training in Human Reproduction was established by the World Health Organization in 1972 to coordinate, promote, conduct, and evaluate international research in human reproduction. The Programme brings together administrators, policy-makers, scientists, clinicians and the community to identify priorities for research and for the strengthening, in developing countries, of research institutions. It marshals the scientific community to conduct research in human reproduction and to evaluate the results of research. The Programme also ensures coordination of efforts in this field and in the exchange of information, joint planning and joint activities among national, non-governmental, and international agencies involved in institution strengthening and research in human reproduction and family planning.

In May 1988 UNDP, UNFPA, The World Bank, and WHO became joint co-sponsors of the Programme.

INSIDE

Sixteen years of collaboration between the Special Programme and The Department of Reproductive Biology, Institute of Nutrition Salvador Zubirán, Mexico City, Mexico*

by
Gregorio Pérez-Palacios

One of the most important components of the broad mandate of the Special Programme has been to support and further develop appropriate national and international resources, particularly in the developing world, for research in human reproduction. To accomplish this objective, over the years the Special Programme has employed a variety of mechanisms including, institution strengthening in its widest context, the provision of research training, the standardization and quality control of laboratory procedures, and the provision of matched reagents for radioimmunoassay among other laboratory supplies.

Collaboration between Mexico, more specifically, between the Department of Reproductive Biology, National Institute of Nutrition Salvador Zubirán, Mexico City, and the Special Programme began with the designation of the Department as a WHO Collaborating Centre in 1972, which was also the first year of operation of the Special Programme. In its role as a WHO Collaborating Centre, the Department identified itself with the Special Programme, giving full support to its early activities which related to: (*a*) the urgent need for extensive studies on the safety and efficacy of existing methods of fertility regulation; (*b*) the development of new and improved contraceptive strategies that could meet the national or regional requirements; and (*c*) the need for institution strengthening for research in this important area of the reproductive sciences. The priority given by the Institute to research on fertility regulation at that time was based on the recognition of the health problems associated with the extremely high rate of population growth in Mexico and on the strong belief that mission-oriented basic research could bring important breakthroughs in this sensitive area of contemporary medicine. Independently, the Department continued to conduct a number of other studies on neuroendocrine regulation of ovulation, sexual differentiation, sexual behaviour, infertility, puberty and menopause.

One of the immediate benefits of collaboration with the Special Programme was the opportunity for the Department to conduct coordinated research with other WHO Collaborating Centres and scientists from both developed and developing countries. The experience of being able to work together in research with those living in far-away countries but facing similar problems was not only instructive but also very rewarding. The staff of the Department gained considerable knowledge from participation in the meetings of principal investigators of multicentre clinical and/or laboratory trials and from the Steering Committees of the various Task Forces of the Special Programme. This experience constituted a learning package on research management which was extensively used at a later stage of the Department's development in the setting up of multicentre studies within the Mexican network of collaborating research centres in human reproduction. The national network includes seven centres at universities and health institutions, all headed by former trainees of the Department.

Through interaction with the Special Programme the scientists at the National Institute of Nutrition learned the value of a multidisciplinary approach to research. Along with teaching, they are now involved in sophisticated basic and clinical (metabolic) research, directing and/or conducting clinical epidemiological trials, doing technical development work, and even learning the complexities of social and communication sciences research in order to incorporate them into the research effort. The De-

**At the Meeting of the Special Programme's Policy and Coordination Committee, held on 4-6 July 1988 in Geneva, Switzerland, Dr Gregorio Pérez-Palacios, Director of the Department of Biology made a technical presentation, describing the nature and results of his Department's collaboration with the Special Programme. This article is extracted from his presentation with his kind permission.*

Issued quarterly by the Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, 1211 Geneva 27, Switzerland. For a free subscription, please write to the above address.

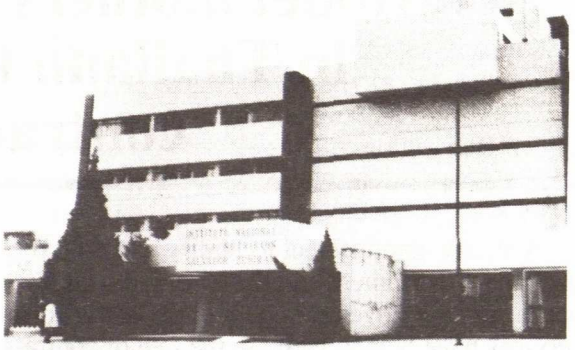
Editor: Jitendra Khanna

partment is proud of having received material support and technical input from the Special Programme.

One of the many factors contributing to the success of the Department in its conduct of research was the assistance provided by the Special Programme in the area of standardization and quality control of analytical laboratory methods. The Department keenly participated in the WHO External Quality Control Scheme on clinical chemistry and in the radioimmunoassays of peptides and steroid hormones relevant to research in human reproduction. The benefit from this was enormous for the Department since through the Scheme adequate tools had become available for the Department to compete in international scientific research. Moreover, the benefit was not limited to the Department alone. Collaboration with the Special Programme provided a new perspective of quality in research, whether clinical or service-related. As a result, the Institute created a new Department of Quality Control, thus becoming the first medical institution in Mexico to have a Department concerned with the quality of the clinical laboratory assays. Interestingly, the Chairman of the Department of Quality Control was himself trained in the United Kingdom under a WHO research training award. At the present time the Institute is actively participating in the establishment of similar quality control schemes throughout the country.

The provision by the Special Programme of well-characterized and standardized matched reagents for radioimmunoassays of reproductive hormones along with the necessary technical expertise, when required, has been another major additional input. Without doubt, the Special Programme's system of supplying matched reagents to research laboratories all over the world is unique, and it would be difficult to replace it. Furthermore, the availability of high quality matched reagents stimulated greater interest in research in this field, which in turn led to an even greater demand for biological reagents; a programme is now underway in Mexico to produce some of the reagents. Indeed, with support from WHO and the Mexican Government the Department has taken the responsibility for producing primary reagents for steroid hormone radioimmunoassay and for the manufacture of corresponding diagnostic kits; a second participant in this programme is the WHO Collaborating Centre in Havana, Cuba, which is in charge of producing kits for peptide hormones. This bi-national programme attempts to cover the increasing demand for these reagents at the regional level.

The introduction of electronic data processing to facilitate clinical and epidemiolgical research activities has also been a major strengthening input from the Special Programme into our Department. The growth and development in this area has occurred in a step-wise manner, beginning with the use of software for hormone assay calculations and reaching up to more elaborated life-table analyses



National Instiute of Nutrition Salvador Zubirán, Mexico City

used in multicentre studies conducted within the Mexican network of collaborating centres. As to the latter, one of our staff is reading a Master of Science course on biostatistics at the University of Reading in the United Kingdom under a WHO research and training award. Thus, the Department will now be able to analyse data from a large pre-introduction WHO-supported study on injectable contraceptives starting soon in three states of Mexico. Once again the benefits of collaboration with the Special Programme have extended far beyond the Department itself to the network of national collaborating centres and to a number of other research and academic institutions of Mexico.

The strict adherence to ethical values in clinical research by the Special Programme in all WHO-supported studies was greatly appreciated not only by the Department but also the entire Institute. Accordingly, the Institute established, sixteen years ago, a committee for the appropriate ethical review of all research protocols following the guidelines recommended by WHO and those by other relevant international institutions. Needless to say, appropriate ethical committees now exist in all centres of the national research network. Moreover, all institutions in Mexico carrying out biomedical research are required by a recently passed law to have proper ethical committees.

Recently, the Department has continued its research and training programme. In the last two years alone, researchers at the Department have published more than 40 papers in major international journals. In addition, the they have written a number of chapters in books, thereby fulfilling the need for disseminating scientific information.

Finally, it may be said that although it is difficult to evaluate in numerical or quantitative terms the impact of the inputs of the Special Programme into our Department, it must be emphasized that the material and technical support furnished by the Special Programme played a critical role in the early development and growth of our Department, and in some areas that of the entire Institute. This support has proved to be the very catalyst that was needed for undertaking our present ambitious programme in research and training in reproductive health. ❑

"Model mothers" motivate women in Thailand to use modern contraceptives

A strong commitment to family planning by the Thai Government and the effective coordination of both governmental and private health services have helped increase the rate of contraceptive use by women of reproductive age in Thailand from 14.8% in 1969/70 to 64.6% in 1984. As a result, the total fertility rate declined by 3 children per woman during the same period: from 6.5 in 1969/70 to 3.5 in 1984.

Currently, a lack of capital and human resources to conduct educational and motivational campaigns, particularly in the rural areas where most of the population lives, is hampering a further increase in the rate of contraceptive use. To see if this problem could partially be overcome by training and using "model mothers" as family planning motivators, the Maternal and Child Health Centre, Ministry of Health, Bangkok, with support from the Special Programme, conducted *A Study on the Use and Effectiveness of Model Mothers as Family Planning Motivators*. There were previous data to show that volunteer workers, when trained appropriately, can deliver family planning services and can motivate people in the community to use them.

The main objectives of the study were: (*a*) to utilize model mothers as family planning motivators in the community by encouraging married women of reproductive ages to accept and/or continue using modern fertility regulating methods; and (*b*) to determine the effectiveness of model mothers as family planning motivators by evaluating changes in contraceptive acceptance rates, and in the proportion of women using modern methods.

To qualify as a model mother, a women had to have experience and knowledge in childbearing and childrearing. Detailed criteria for selection were:

1. pregnancy between the ages of 20 and 30 years;
2. at least two years of pregnancy free interval between births;
3. low parity;
4. having had early antenatal care and having had deliveries aided by health personnel or trained traditional birth attendant;
5. having had all basic vaccinations, including two cycles of tetanus toxoid vaccination;
6. having correctly practised self-care during pregnancy and at the time of and after delivery;
7. having had children with birth weight not less than 2.5 kg;
8. having breast-fed her children for not less than 12 months and having started suppplementary feeding correctly; and
9. having had children with normal growth and development, e.g. no malnutrition and normal weight according to age.

The study was undertaken in a rural community in the north-east region of Thailand. In order to evaluate accurately the impact model mothers might have in a community, two demographically similar villages were chosen, one of which served as control. The population in both villages had a low socioeconomic status and could be considered representative of rural Thailand. A pre-test survey was undertaken to gather baseline information and to determine who were the users and non-users in both villages. Five to seven model mothers were recruited in the experimental village using the above criteria. They were given a five-day training course in population problems, modern fertility regulating methods (availability, action, side-effects, etc.), health education, communication and motivation skills, record-keeping, and referral systems. Once trained, the model mothers visited married women of reproductive ages in every household over one year to motivate them to use modern fertility regulating methods. In the control village there were no model mothers. But the health services functioned normally in both villages.

Following the intervention period, a survey was conducted to determine the effectiveness of model mothers by comparing the two areas in terms of increase in the contraceptive acceptance rate, increase in proportion of users using more effective methods and increase in the number of mothers who fitted the above criteria for selecting model mothers.

The survey revealed that the contraceptive

acceptance rates in the experimental area were significantly higher than those in the control area. Most of the women in the target group were found to have a positive attitude towards model mothers. Analysis of contraceptive acceptance data by age showed that previous non-users in the 20-29 age group (same age group as the model mothers) had the highest acceptance rates, most probably because of friendship and intimacy between the model mothers and other women of their age group. On the other hand, previous non-users of the 15-20 age group who became new acceptors had low continuation rates because some of them had got married in the meantime and wanted to have children. There was a low acceptance rate among older women (30+). This was attributed to the attitude among these women that they should not follow the advice of their juniors. However, on the whole it was found that the new users were influenced more by the example of model mothers than the motivational activities of the health officers.

The project clearly demonstrated that model mothers can help significantly in not only motivating women to use modern contraceptives but also in promoting health activities in general, for example, improving nutrition and basic immunization. In rural areas of Thailand, where the reach of the mass media remains limited and the goals of the government family planning programme have been only partially attained, community participation has an important role to play in the promotion of family planning and of the use of modern contraceptives. ❑

Source: CHUTIMA SIRIKULCHAYANONTA (1984) *A Study on the Use of Model Mothers as Family Planning Motivators in a Thai Rural Village.* Bangkok, Bangkok Maternal and Child Health Care Center (Report of a WHO-sponsored research project).

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in the blood; this raised the possibility that vasectomy might trigger certain autoimmune diseases. Secondly, in the late 1970s there were reports of accelerated atherosclerosis (hardening of blood vessels) in vasectomized monkeys. These studies were rapidly followed by epidemiological studies of vasectomized men in the Western countries (where the incidence of cardiovascular diseases is high), which did not find a similar association in man.

The Sichuan Study

The province of Sichuan is the most populous province in China. It has a very high number of vasectomized men. Among some 100 million people in the province, approximately 10 million men have undergone vasectomy during the past 20 years.

The study was conducted on a total of 8936 men, of whom 4596 (51%) were vasectomized. The mean age of both vasectomized as well as non-vasectomized men was 52.3 years. In contrast to some of the earlier epidemiological studies, the mean duration of vasectomy in this study was as high as 14.5 years, with a range of 10-25.4 years.

No significant differences were found among the two groups with respect to height, weight, blood pressure or cholesterol concentrations. In response to direct questions, fewer vasectomized men reported specific illnesses compared to non-vasectomized men. This was particularly true for hypertension, heart disease, rheumatism, and asthma. It should be pointed out here that the prevalence of cardiovascular disease in Sichuan is generally low. Thus the results of this study show that vasectomy has not altered the existing low risk of cardiovascular disease.

As is the case with other studies of this kind, it was not possible to eliminate all bias from the study. The investigators concede that even though vasectomy is an extremely safe surgical procedure, screening and selection for it may tend to select healthier men; hence the observation that vasectomized men are healthier. While all studies conducted so far suffer from this problem, the influence of this factor may be somewhat greater in the present study since there is a high prevalence of vasectomy in Sichuan. None the less, this study has further strengthened the available evidence[1] in favour of a lack of association between vasectomy and cardiovascular and other diseases. ❑

[1]MASSEY. F. J., ET AL. (1984) Vasectomy and health: results from a cohort study. *Journal of American Medical Association*, **252**: 2315-2317.
PETITTI, D. B. (1986) Epidemiologic studies of vasectomy. In: *Male contraception:advances and future prospects*. G. I. Zatuchni, et al., eds. Philadelphia, Harper and Row.

2nd Basic Science Symposium

Focus on growth regulatory factors for new leads in fertility regulation research

A symposium on "Potentials of Molecular Biology in Fertility Regulation: Growth Regulatory Factors" was convened in Bethesda, MD, USA, on 22-24 September 1988. Second in the Special Programme's series of Basic Science Symposia, this meeting was organized in collaboration with the Center for Population Research of the National Institute of Child Health and Human Development, Bethesda, MD, USA.

The main purpose of this Symposium was to review current knowledge on the molecular biology of the growth regulatory factors–particularly their role in reproduction–in order to identify new potential leads for developing new fertility regulating methods. It has been known for some time that various types of cell produce specific polypeptide substances which act predominantly locally, either on the very cells that produce them (autocrine action) or on the surrounding cells and tissues (paracrine action). As the name implies, the prime function of growth regulatory factors is to stimulate or inhibit the growth of cells. However, they are also involved in the regulation of certain other cellular functions.

The evidence presented at the Symposium confirmed that a number of growth factors and related substances influence (by both autocrine and paracrine means) gonadal function in humans as well as in animals. But since most of these substances also have important functional effects in tissues other than those in the gonads, they are regarded as difficult targets for "contraceptive attack". (Substances whose effects are limited to the reproductive tissues only are generally better and easier targets.)

Four promising areas of research were none the less identified. The first relates to the process of cell division in the gonads (called meiosis), which gives rise to spermatozoa and eggs. Meiosis is unique in that the daughter cells (spermatozoa and eggs) end up with half the number of chromosomes than in the original cell. Another unique attribute of meiosis is that during its course there appear certain proteins which have not been found to be present during mitosis, the other, more common, form of cell division, in which the a cell replicates itself, producing a full complement of chromosomes in the two resulting cells. One such protein, which is synthesized during meiosis as a result of the expression of a gene called "c-mos proto-oncogene" could be a potential target for "contraceptive attack".

A second group of possible targets was considered to be the factors controlling the growth and development of blood vessels (angiogenesis) in the ovary and the inner lining of the uterus (the endometrium). Although the formation of new blood vessels occurs at various times in different tissues of the body (e.g., during the healing of a wound), the process of angiogenesis in the ovary and the endometrium is unique since it follows a cyclical pattern linked to the menstrual cycle.

The third area identified for further research relates to the interaction between the reproductive and the immune systems. It is now well known that certain immune cells (macrophages, lymphocytes, etc.) produce protein products called interleukins which exert effects on the reproductive tissues in addition to their immunological functions. For example, it has been reported that a protein called interleukin-1, which is produced by macrophages located in the reproductive organs, is capable of, inter alia, inducing the production of prostaglandins–substances known to cause uterine contraction. Interleukins have also been reported to be involved in the early processes in the production of sperm (spermiogenesis), sperm motility, fertilization, development of the embryo, and pituitary function.

Fourthly, following discussion on the structure of the receptors for growth factors and other hormones, it was suggested that interference with the binding sites of certain receptors might yield another approach to fertility regulation. For example, this might be achieved by the synthesis of organic compounds capable of binding with the receptor but without any biological activity. In this regard the receptor for the follicle stimulating hormone (FSH) appeared to offer the most promise owing to its specificity and relevance to fertility regulation.

Finally, since the immune system appears to have effects on reproductive function, and the Human Immunodeficiency Virus (HIV) infection affects the immune system, further research on the molecular biology of the reproductive and immune systems will be relevant also in the context of the possible interaction between steroidal contraceptives and HIV infection.

The full proceedings of the Symposium are to be published soon by Cambridge University Press as volume 2 of the series: Basic Science Topics in Fertility Regulation Research. ❑

New strategies proposed for the study of breast cancer and the pill*

Millions of women throughout the world have used, and continue to use, the contraceptive pill. But since its introduction, there have remained some doubts about its long-term effects, including cancer; concern about the risk of breast cancer in particular has been great since it is the most common type of cancer among women. However, only recently has it been possible to assess in any meaningful way the relationship between the use of the oral pill and the risk of developing breast cancer. With the use of the pill rising in many developing countries, the need to assess the association between the pill and breast cancer has acquired a new urgency.

In general women who have used the pill do not seem to have any different risk of breast cancer as compared to those who have not used the pill. However, when selected subgroups of women are looked at separately, (e.g., young women) recent studies show conflicting results.

Studies published so far on this subject have been remarkably consistent with respect to the overall effect of oral contraceptive use on breast cancer risk. In general women who have used the pill do not seem to have any different risk of breast cancer as compared to those who have not used the pill. However, when selected subgroups of women are looked at separately, (e.g., young women) recent studies show conflicting results, with some finding a link between early long-term use of oral contraceptives and an increased risk of breast cancer and others not. This lack of consistency is puzzling for both epidemiologists as well as family planning experts.

To help understand the reasons for variations in results and to propose a research strategy that would clarify the relationship between oral contraceptives and breast cancer, WHO's Special Programme of Research, Development, and Research Training in Human Reproduction convened a meeting of scientists_ with relevant experience and epidemiological data on the subject. At the meeting, available epidemiological data were reviewed, including recent, still unpublished data. Possible explanations for the varying findings were discussed and a number of research strategies were proposed.

The participants at the meeting found the new, yet unpublished, data presented at the meeting to be striking in their lack of consistency between studies. As with the published data, some of the studies showed an increased risk of breast cancer among selected subgroups of women, whereas other studies found either no change in the risk among any subgroups studied or an increased risk among different subgroups. A large number of hypotheses were offered as possible explanations for the apparent lack of consistency, but none of them was sufficiently convincing so as to inspire a consensus among the participants at the meeting. However, the scientists agreed that three of the hypotheses merited further consideration.

According to the first hypothesis, the variations between the findings may be attributable to differences in the length of time the pill has been in use in the study populations. Thus, it could be that the pill does increase the risk of breast cancer, but that such a risk is observable only after a given population has used it over a long term, for example, for 15 years or more. It would follow then that the studies that have found no risk of breast cancer associated with the use of the pill have examined populations in which the pill has not been in use for a sufficiently long time.

The second hypothesis pertains to the changing types and levels of hormones in the pill over time. It is known that estrogens and progestogens have different effects on breast tissue, and could have different effects on the risk of breast cancer. Furthermore, different types of progestogens or estrogens, or their relative amounts, could play a role in affecting breast cancer risk. The specific hormone content of oral contraceptives has changed dramatically over time, although not consistently around the world. The discrepancies between studies might thus reflect different patterns of hormone content of the pills used by the populations studied.

The third hypothesis relates to bias as a possible explanation for discrepant findings. The types of bias considered most likely to play an important role in the findings reviewed at the meeting were information bias (or recall bias), bias in the selection of study subjects, and in their surveillance and follow-up.

Suggested research strategies

Given the lack of any conclusive evidence, the Group recommended additional research. First the

Continued on page 8, see **Cancer**

**From the report (unpublished) of a Meeting on Breast Cancer and Oral Contraceptives, Geneva, 27-28 June 1988.*

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group felt that studies in basic sciences could contribute much not only to the elucidation of the epidemiological data but also to the understanding of the nature of an association, if any, between the pill and breast cancer.

Secondly, the interpretation of the epidemiological data is hampered by a lack of biological data which could be used to classify the numerous pill preparations that have been used over the past 20 years. Most biological classifications of the pill's estrogen and progestogen content relate to their effects on the uterus rather than the breast.

Thirdly, since oral contraceptive use is so widespread, any effect on breast cancer risk should be apparent in trends of breast cancer incidence and/or mortality. Although reliable data would not be available from all countries, it was thought useful to look at the relationship between patterns of oral contraceptive use and trends in breast cancer incidence and mortality. Another approach suggested was to develop models that would predict the effects on cancer incidence, given different hypothetical relative risks, latency periods, and oral contraceptive use patterns.

Fourthly, although most epidemiological studies on oral contraceptives and breast cancer have information on specific pill preparations, data on any one preparation is usually minimal, thus limiting the conclusions that could be drawn about specific preparations. It was suggested that a ranking system be developed so as to compare the results from the various studies and to look for consistent trends with respect to pill preparations.

Although numerous epidemiological studies have already been undertaken on the association between breast cancer and oral contraceptives, it was agreed at the meeting that there may be a need for further case-control studies in the future as patterns of use and pill preparations change. However, it was clear that such studies must be virtually bias-free, both in order to achieve credibility as well as to add new information to the large body of available knowledge on the subject.

Finally, the consensus of the meeting was that the epidemiological data continue to lack consistency, and epidemiologists are hampered by an apparent lack of biological data on which to base hypotheses to explain the lack of consistency. Thus, while encouraging more basic research, it is essential that epidemiologists interact closely with scientists working in other relevant areas. It is critical that scientists involved in basic research be familiar with the issues raised by the epidemiological studies, and at the same time that epidemiologists be aware of important findings in basic science research. ❑

New Publications

Now available from the Medical Research Council of Canada

Towards an International Ethic for Research with Human Beings; Proceedings of the International Summit Conference on Bioethics April 5-10, 1987, Ottawa, Canada

and

Towards an International Ethic for Research with Human Beings/ Pour une éthique internationale en recherche sur les sujets humains; Documents

The fourth International Summit Conference on Bioethics was held in Ottawa, Canada, on 5-10 April 1987. It was sponsored by the Medical Research Council of Canada and the Department of National Health and Welfare. The participants included twenty-six leading authorities, nominated by the heads of state of the Economic Summit nations, by the European Economic Community, and by the World Health Organization.

The first publication is a summary of the proceedings of the Conference. The second is a collection of background articles commissioned for that meeting. The books contain the Conference's reflections on the policies adopted in recent years to limit research on humans and recommendations on ways of improving the protection of the subjects of research throughout the world.

To obtain these publications free of charge please write to:

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