Chapter 3

WAS IT A RESEARCH PROPOSAL?

Well before the formal start of the hearings, a debate had begun on whether or not the 1966 Proposal was research. It was provoked in part by the magazine article which had precipitated the establishment of this Committee of Inquiry. My Terms of Reference also require me to answer the question, "Was there a research programme...?"

The article was entitled "An 'Unfortunate Experiment' At National Women's". The phrase "unfortunate experiment" was taken from a letter written by Professor David Skegg of the Department of Preventive and Social Medicine at the University of Otago and published in the New Zealand Medical Journal early in 1986. In that letter, obviously part of a continuing correspondence on cervical screening, Professor Skegg had written:

> "The case for the effectiveness of [cervical] screening does not rest on the unfortunate experiment at National Women's Hospital, in which women with abnormal smears were treated conservatively and a proportion have developed invasive cancer."

By the time the Inquiry hearings were underway the 'research' debate was intense. It was raised by a number of witnesses early in the proceedings. Some took the view that it was not a research proposal but a move to treat patients more conservatively. Others were clearly of the view that it was a research proposal, albeit a poorly designed one. The terminology used to describe the 1966 Proposal included – research with the intention to cure, human experimentation, trial, move to more conservative treatment, clinical cartography, observational research, clinical research, special series project and research programme.

It is important, therefore, to set out some technical information on the terminology of medical research, particularly as it applied in 1966, and the scientific and ethical considerations which surrounded it. I received much helpful information from experienced medical researchers, from ethicist Professor Alistair Campbell, and from the Director of the Medical Research Council of New Zealand, Dr James Hodge. Their evidence provided the technical and conceptual framework within which to measure the 1966 Proposal and assisted greatly with the definition of terms.

DEFINITIONS OF RESEARCH

I do not intend to set out a detailed description of the design of research proposals. This section is intended to explain the definitions I have used for the purposes of my report and those scientific and ethical criteria which I accept as appropriate to research design in 1966 and for the duration of the Proposal.

Medical research can entail the observation of recorded data only, with no intervention in the treatment of a patient. At the other extreme, it can be termed 'human experimentation' and involve intervention in the course of the disease. Such human experimentation can be therapeutic and thought to be of benefit to the patient; or non-therapeutic and therefore assumed to be of no direct benefit to the patient.

Medical research implies a systematic and organised activity which clearly goes beyond normal service or treatment requirements and which has the potential to advance knowledge in a field relevant to human health. 'Organised' implies prior planning, perhaps with the formulation of a testable hypothesis or aim.

Research programme

The 1966 Proposal was occasionally referred to as a research programme during the hearings. The phrase was also used in my Terms of Reference. The latter instance in particular prompted Dr Hodge to comment on its definition. He said:

> *"'Research programme'...is not a precise term, being used to describe grouped research activities in a number of different contexts.*
>
> *"Sometimes the terms 'research project', 'research programme' and 'study' are used synonymously. The MRC* [Medical Research Council] *has a specialist definition of the term 'research programme' to define a group of interrelated research projects being conducted by a group of investigators, possibly eligible for more broadly-based funding than that provided under a single project grant."*

For the purposes of this Inquiry I have treated the word 'programme' as synonymous with a single trial. During cross-examination Dr Hodge also said that 'study', 'trial' and 'experiment' could be used synonymously.

Observational research

A fundamental criterion for observational research is that no action is taken by the investigator to alter the conditions under study. Observational research may be prospective (that is the study progressing with time), or retrospective (studying events in the past).

Experimental research

In experimental research the conditions of the study are determined and maintained by the investigator in such a way that he or she does not merely observe what is going on, but intervenes. Experimental studies are therefore called intervention studies. They are always prospective.

When the aim is to evaluate the outcome of different methods of treatment, experimental studies are often called clinical trials. In a clinical trial, the intervention involves the administration of a new treatment to one group of patients or, less commonly, the withholding of conventional treatment. The experimental group of patients is usually compared, though by no means always, with a control group receiving standard treatment. The term 'clinical' is used to denote activities taking place within the context of the patient-doctor relationship.

If it is ethically and logistically possible to divide patients into the two groups at random, the study is described as a 'randomised controlled trial' and this is generally regarded as the most scientifically rigorous method available for testing the efficacy of new therapeutic measures or preventive measures. Ethically, it is imperative to obtain a patient's consent, not only to be included in the trial but also to be randomised. The randomised controlled trial was far less common in 1966. Dr Green's Proposal could not be defined as such, although in his 1974 paper[1] he had described it as

> "the nearest approach yet, to the classical method of deciding such an issue as the change or not of a disease from one state to another – the randomised controlled trial".

The Declaration of Helsinki 1964 (and its revisions in 1975 and 1983) make a distinction between clinical research combined with professional care (therapeutic research) and non-therapeutic clinical research. The former is defined as 'research in which the aim is essentially therapeutic for a patient'. Therapeutic research could be the comparison of the standard management of patients with a new method of management. In such a trial the balance of risks and benefits to be assessed should be no greater than those of the standard management. Non-therapeutic research is defined as:

> "Research, the essential object of which is purely scientific and without therapeutic value to the persons subjected to the research."

An example would be the testing of a drug on volunteers for whom the drug is expected to offer no benefits.

Obviously there can be some difficulty in defining the precise point at which good clinical practice involving systematic observation warrants a research label; or the point where routine medical therapy, perhaps using procedures which are still in the process of development, becomes experimental research. Nevertheless, in both instances there will be aspects which clearly identify a research component, even in the absence of a well-designed study protocol. There will be a **clear intent** on the part of the investigator which involves more than the observation or management of individual patients. There will be a **statement or the inference of an hypothesis,** (something which the investigator is attempting to prove or disprove). Finally, in experimental research there will probably be **evidence of advanced planning** for managing a clearly identifiable group of patients by methods which differ from the way in which other patients with the same disease are managed.

WAS THE 1966 PROPOSAL RESEARCH?

In order to resolve the treatment/research question I have sought to identify the 1966 Proposal's aim. I consider the aim, hypothesis, or intent of the Proposal is the best means of distinguishing whether or not it was intended only as a means of treating patients or whether it had a research component.

After reviewing a variety of criteria and evidence, I have come to several conclusions. In terms of the 1964 Declaration of Helsinki it was clinical research combined with patient care. It was an experimental study, not a retrospective observational trial. The 1966 Proposal **was** a research proposal with the aim of advancing medical knowledge.

1. The aim of the Proposal

The discussion recorded in the Senior Medical Staff Minutes states:

> "Professor Green said that his aim was to attempt to prove that carcinoma in situ is not a premalignant disease."

I have already dealt with the assertion that this was an incorrect report of the aim as he stated it.

The stated aim clearly demonstrates that in Dr Green's mind this was a research proposal. Dr Green was an enthusiastic clinician and academic. He was always open about his work and he published prolifically on CIS. I have read and heard evidence about most of his scientific papers on this subject published from 1962 to 1974. Even before the 1966 Proposal was approved it is clear from his published work that Dr Green, with a clear aim in view, was studying patients who continued to have positive smears. In his 1964 paper, 'Cervical Carcinoma in Situ: True Cancer or Non-invasive Lesion?'[2] he says:

> "In the present paper it is proposed by adducing clinical, indirect statistical and experimental evidence, to show that the lesion is probably benign in the great majority of cases."

This paper reviews a series of 278 patients with CIS, 190 of whom had been reported on by Dr Green in 1962. Of the 278 patients, 151 had been treated by hysterectomy and the remaining 127 by local excision. Two years later in 'Cervical Carcinoma in Situ'[3] Dr Green says:

> "In this Paper it is proposed to question further the correctness of the claims that in situ cervical cancer is a serious lesion because of its invasive potentialities and that cytology by revealing it can eliminate invasive cervical cancer."

This paper reported on a series of 446 cases which was an extension of the 276 referred to in the 1964 paper. Sixty per cent of these patients had been treated by local excision of the lesion and the remainder by total hysterectomy. His aim, therefore, was set out clearly in material written before the 1966 Proposal was approved. The 1966 Proposal simply referred to an expanded number of the same group mentioned in both papers.

The purpose of the Proposal also appears in papers published after its approval. Another paper co-authored by J W Donovan, a medical statistician, and titled 'The Natural History of Cervical Carcinoma in Situ'[4] was published in 1970. Natural history is a term used to describe the stages in the process of a disease – its progression, remission and final outcome, unmodified by therapeutic intervention (treatment). The authors say:

> "There have been many previous studies of the natural history of carcinoma in situ of the cervix, based on observations of series of patients. Some, like the present report, concern patients selected prospectively."

That same year, in a paper 'Cervical Carcinoma in Situ'[5] Dr Green said:

> "The only way to settle the question as to what happens to carcinoma in situ is to follow adequately diagnosed but untreated lesions indefinitely. This is a theoretical impossibility because diagnosis is always treatment to an indeterminate degree. However, it is being attempted at National Women's Hospital by means of two series of cases."

These later papers, therefore, also show that Dr Green himself continued to regard his work as a study deliberately initiated to test a theory, namely the probability of progression of an in situ lesion to invasive cancer.

There were other sources that reinforced this finding.

a) From about 1964 the Medical Research Council was receiving applications from National Women's Hospital for research programmes including a study of carcinoma in situ. In 1982, during a visit to the Hospital, the project on CIS was reviewed by the Medical Research Council.

b) In 1968, in the annual report of the Postgraduate School of Obstetrics and Gynaecology at National Women's Hospital in a subsection entitled 'Research', a study sourced to G H Green says:

> "Carcinoma in situ. The relatively benign nature of so-called 'carcinoma-in-situ' has now been established with confirmation from studies of fetal and neonatal cervix from necropsy material. In order to pursue this matter further, epidemiological comparisons are being made with invasive cancer cases."

c) In 'Antigenic Relationship between Cancer of the Cervix and Carcinoma in Situ', an application to the Medical Research Foundation for a grant, Dr Green listed his most important and recent research publications. The application included references to the 1969 paper 'Invasive Potentiality of Cervical Carcinoma in Situ' and the 1970 papers 'The Natural History of Cervical Carcinoma in Situ' and 'Cervical Carcinoma in Situ', which had been given the editorial subheading, 'An Atypical Viewpoint'. All these papers were produced during the Inquiry and examined in some detail.

I agree with Dr Jordan's summary of the 1966 Proposal:

> *"The aim of the trial, which is what it was, was therefore to establish a diagnosis of carcinoma in situ but to leave the patients without treatment. This was contrary to generally held beliefs at that time."*

2. Other indications that it was a research proposal

(a) In spite of the fact that his own papers described the Proposal in terms such as

> "There have been many previous studies of the natural history of carcinoma in situ of the cervix based on observations of series of patients. Some, like the present report, concern patients selected prospectively"

Dr Green denied during the course of the Inquiry that the 1966 Proposal represented a research project. His initial assertion was that:

> *"There wasn't a research programme at the hospital. It was the hypothesis of mine that very few in situ cancers ever went on to invasion, because otherwise certain national and international statistics could not be substantiated. Either the theory or the observed facts, or both were wrong."*

Dr Green was understandably anxious that I might draw the inference that patients were being used as 'guinea-pigs'. He was also concerned at the suggestion that the research project had as its corollary, the absence of intention to cure patients. In spite of statements to the contrary in his 1970 and 1974 papers, Dr Green was also reluctant to concede that it was a prospective study.

The debate was intense but eventually Dr Green conceded that the 1966 Proposal was a research programme into the natural history of carcinoma in situ. He emphasised, however, that there was always an intention to cure patients. Nevertheless, counsel for another party, under cross-examination, succeeded in persuading him to return briefly to his original assertion that it was not research.

Dr Jordan's summation of the Proposal in practice was brief:

> *"One gets the impression that Professor Green never referred to this as being research but* [as] *clinical observation, and he refers repeatedly to treatment with punch biopsy. Now that begs the question, because the procedure which was adopted, namely a punch biopsy with a view to leaving carcinoma in situ, is not treatment, and if that is the case then it is a trial. It is not simply an observation."*

(b) When Dr Green published his last paper specifically on the invasive potential of CIS, in 1974, he said:

> "This series of 750 cases of insitu cervical cancer, and the following of 96 of them with positive cytology for at least two years, represents the nearest approach yet to the classical method of deciding such an issue as the change or not of a disease from one state to another – the randomised controlled trial. It has not been randomised and it is not well controlled but it has at least been prospective...
>
> "Quite apart from [the] technical difficulties in creating a randomised series to test the progression theory, there are those problems which arise from the almost universal application of the principle of early diagnosis and prompt treatment of cancer – even though there may be some doubt about the actual diagnosis."

In retrospect Dr Green himself saw the limitations of the 1966 trial. In the same 1974 paper he wrote:

> "As a result of the experience in the present limited effort at demonstrating the natural history of in situ cancer it is considered that it is probably technically impossible to create a randomised controlled series to demonstrate the progression or otherwise of in situ cancer to invasion. Carcinoma in situ is a histologic and not a clinical state and must be so diagnosed, but because of the variability possible in a highly subjective field it is not possible ever to be completely certain of the diagnosis (i.e. that it is not invasive) unless the whole lesion is completely extirpated – in which case the 'trial' is already concluded. If a less-than-complete excision biopsy is practised, pathological doubts are immeasurably increased and cannot

be altogether dispelled by calling on aid in the exclusion of invasion from cytology itself, or colposcopy, or even careful clinical examination.... The pressures against instituting a truly randomised controlled trial in this direction, even although widespread doubts about the probability of progression of in situ lesions be conceded, are daunting to say the least."

(c) I believe Dr Green was so confident that CIS was almost always a harmless disease that he felt quite sure his methods would not put his patients at risk. He was studying the disease and publishing the results so that he could convince the rest of the world that his theory was correct. As he wrote in his 1970 paper, 'Cervical Carcinoma in Situ':

"Obviously such prospective studies on carcinoma in situ as those detailed above can only be done by those who are unconvinced of the invasive potentiality of this lesion."

RESEARCH PROJECT OR NEW TREATMENT PROTOCOL –

Significance for the patient

At this point there is an overriding principle which needs immediate emphasis. Regardless of whether the 1966 Proposal put to the Hospital Medical Committee was a research project with implications for the treatment of a class of patients, or a new treatment protocol which might produce valuable information and advance medical knowledge, the ethical implications for the patients were very similar. As Dr Hodge said:

"I would argue that clinical research is only one aspect of the many activities relating to the care of patients which require high ethical standards of conduct. Although research is the most visible of these activities, and the one most clearly in need of regulation, it should not cause us to lose sight of other areas in which the protection of patients may be of equal or even greater importance.

"Uncritical or outmoded practices in patient management, although falling well short of overt malpractice, may place individual patients at greater risk than a supervised clinical experiment. It follows from this argument that whether or not a clinical practice is defined as research is unimportant. In my view it should be subjected to normal peer review and its ethical implications should also be discussed in an organised manner."

Both treatment and clinical research, therefore, require similarly high ethical standards to be observed. There is no reason for any patient to resist being included in a properly planned research protocol on the grounds that she might be harmed. Professor Skegg said:

"It is my sincere view that with appropriate safeguards patients included in clinical trials should have nothing to fear and may indeed benefit from the special attention they receive."

He also said:

"...It would be a mistake for us to have the impression that departing from conventional treatment in the course of a trial is somehow inherently worse than a doctor departing from treatment because he is out of date or an alcoholic or something like that.

"In general such departures are less hazardous in clinical trials because the patients will be closely followed up and the trial should be stopped if anything goes wrong."

DESIGN OF THE 1966 RESEARCH PROPOSAL

It is useful to measure the 1966 Proposal approved by the Hospital Medical Committee against research standards in 1966. The Medical Research Council received research

proposals from various groups during 1966 and in evidence Dr Hodge said that those proposals generally

> *"provided information which was more adequate* [than that found in the 1966 Proposal] *for scientific assessment, under such headings as specific aims of the research, significance of the research, previous work by the applicant, results obtained by others and facilities available for conduct of the research."*

The research community has methods of defining research. When Dr Hodge was invited to comment on the written 1966 Proposal he said:

> *"...the report itself is quite brief and does not qualify for description as a formal research proposal. While it states a research hypothesis (that CIS is not a pre-malignant disease), it is largely confined to criteria for subject inclusion and is lacking in details of study design and material essential for its evaluation as a research protocol."*

By Medical Research Council standards then, the 1966 Proposal lacked certain key elements. As this was a proposal which required the inclusion of human research subjects, I also consider that there were some critical flaws or omissions. The first of these was the lack of a termination date. For example, that date could have been the point at which the treatment of a sufficient number of patients had been observed over a set period. It was also critical that the investigator had already established in his own mind that the study would be terminated if the emerging results demonstrated that the patients were at risk.

Proper design of a research proposal must ensure that the question being posed can be answered and that the hypothesis can be proved or disproved. The hypothesis in the 1966 Proposal was that carcinoma in situ was not a premalignant disease. If the hypothesis were disproved, however, then there were major risks for the patients involved. Furthermore, Dr Green had to be sure that the woman did not have undetected invasive cancer at the point when she was included in the trial; if he could not do that, he could not test his hypothesis.

Before the current Inquiry was contemplated, Professor Skegg wrote in the January 1986 issue of New Zealand Medical Journal:

> "The case for effectiveness of screening does not rest on the unfortunate experiment at National Women's Hospital, in which women with abnormal smears were treated conservatively and a proportion have developed invasive cancer. But Green tries to dismiss these results as being due to either inadequate exclusion of invasion at the outset or over-diagnosis of invasion later. The latter explanation is hardly credible in the case of those women who have died from their disease and the whole argument betrays circular thinking. If the experiment was incapable of falsifying Green's hypothesis, why was it carried out? Moreover, if invasion could not be excluded confidently at the outset, were the patients warned of the risk that was being taken?"

THE ETHICAL PERSPECTIVE

The 1966 Proposal approved by the Senior Medical Staff and the Hospital Medical Committee contained no specific provision for obtaining consent of any of the patients included in the trial. The matter was not discussed at either of these meeting and I have seen no consent to inclusion in such a trial in any patient's file. The patients who gave evidence and who were identifiable as being Group 2 patients, did not mention any procedure whereby their consent to inclusion was sought verbally. However, several of them were intuitively aware of being research subjects. The term 'guinea-pig' was commonly used when describing the many years of repeat visits to the Hospital for further examinations.

Only one patient (Code 5R1) stated decisively that she had known she was part of a research trial. She said that when she first saw Dr Green:

"He said to me that it was a precancerous smear but he didn't think it was going to develop and would I join A-team and he would like me to come in at specific intervals to check me. And I agreed to that and he also removed the coil at the same time."

Question: *You said that he asked you would you join his A-team?*

Answer: *Yes.*

Question: *What did you understand that he meant by that?*

Answer: *Well obviously a group of women that he was going to research and put together some sort of information that could possibly prove that what I had had on the smear was not going to develop. That's what he told me.*

Question: *Did he tell you that?*

Answer: *Yes.*

Question: *Was the word 'research' used?*

Answer: *That's the word I have in my mind, but it's that far back in my memory I couldn't positively say that was actually it. I do remember the A-team very well, and I might have interpreted what he was going to do was possible research and I did appreciate that...looking into something takes a long time. But whether or not he actually said that word I couldn't positively say.*

Question: *Were you asked to sign any form or give any form of consent?*

Answer: *Not to my knowledge. I don't remember that, no.*

Question: *Did Professor Green tell you that other doctors or hospitals may treat people with your sort of smears differently?*

Answer: *No.*

Question: *Did you at any time think that you were being treated differently from anybody else with that sort of smear?*

Answer: *No, I didn't get that impression. He was treating me and that was that.*

In fact this patient had only sketchy information about the nature of the trial she was being included in and was not given the essential information that, as a consequence of being part of the trial, the treatment she was being offered was not conventional.

In 1966 the doctrine of 'informed consent' was far from developed in New Zealand. (It will be more fully discussed in later chapters.) Morally and professionally, however, the requirement to obtain consent to inclusion in a non-therapeutic trial had been clearly stated in the Nuremberg Code of 1947, which said:

"The voluntary consent of the human subject is absolutely essential."

In 1964 a draft Code of Ethics on Human Experimentation was accepted at a meeting of the World Medical Association in Helsinki. It is now known as the 1964 Helsinki Declaration. Where the research is clinical research combined with professional care (a therapeutic clinical trial), the Helsinki Declaration stipulated:

"1. .... If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation."

CONCLUSIONS

It has been suggested that the 1966 Proposal was not a research project because of its inadequate design; because disproving the stated hypothesis posed risks to the patient;

and because it totally overlooked any requirement to inform the patients involved and seek their consent to be included. I cannot accept that suggestion. While I agree that the 1966 Proposal lacked a number of important design characteristics, I reiterate the principle of primacy of aim. A poor design does not change the intention. Nor did it, in fact, prevent a flawed research protocol being put into place and allowed to continue for many years, without intervention and with no provision for termination. The only possible therapeutic value that I can extrapolate from the 1966 trial is that patients might have been saved the procedure of cone biopsy. As it happens, this was not achieved, except in a very, very few cases.

It was an attempt to prove a theory that lacked scientific validity and little attention was given to ethical considerations. From 1966 and throughout the period of the 1966 trial, there were clear guidelines against which a doctor's moral and professional right to include patients in research trials could be measured. I can think of no reason for gynaecologists who practised at National Women's Hospital or in other parts of New Zealand, or administrators whose responsibility it was to be familiar with ethical principles, to overlook the basic ethical and scientific information that was then available.

The fact that the women did not know they were in a trial, were not informed that their treatment was not conventional and received little detail of the nature of their condition were grave omissions. The responsibility for these omissions extends to all those who having approved the trial, knew or ought to have known of its mounting consequences and its design faults and allowed it to continue.

1. 'The Progression of Pre-Invasive Lesions of the Cervix to Invasion', The New Zealand Medical Journal, Oct 9, 1974, 280, 285
2. Australian & New Zealand Journal of Obstetricians & Gynaecologists (1964) 4:165.
3. American Journal of Obstetrics and Gynecology, April 1, 1966,
4. Journal of Obstetrics and Gynaecology of the British Commonwealth.
5. Australian and New Zealand Journal of Obstetrics and Gynaecology