Chapter 2

1966 PROPOSAL IN OPERATION

The management of patients over the years since the 1966 Proposal deserves special attention. This section looks at particular aspects of that management. There also has been some confusion over whether techniques were solely diagnostic, were treatment, or on occasions a combination of both; and whether this was by chance or by design. I shall therefore comment on terminology as well where appropriate.

THE PUNCH BIOPSY SERIES

A punch biopsy is defined as a small piece of tissue approximately 5mm in diameter taken from a part of the cervix for microscopic examination. All overseas and most New Zealand authorities agreed that this biopsy technique has never been accepted as a form of treatment. Dr Jordan confirmed that a punch biopsy has been regarded solely as a diagnostic procedure throughout the period with which this Inquiry is concerned (1966-1987). However, Professor Richart and Dr Jordan said that it was possible that a punch biopsy might eradicate a very small lesion.

Dr Laverty, a specialist gynaecological histopathologist and cytologist practising in Sydney, Australia, noted that small punch biopsies are a "particular area of concern". While he agreed that by 1960 a single punch biopsy could "excise a very small lesion completely, or alternatively be followed by a so-called 'spontaneous cure' of small CIS lesions", if it was intended to use this technique as treatment, then the correct siting of the punch using a colposcope was of paramount importance. Obviously, to be adequate treatment, the lesion should be seen to be removed in its entirety.

None of the independent authorities took the view that a clinician ought to use the single punch biopsy as a treatment technique.

On occasions, a clinician may choose to use a series of punch biopsies, usually known as multiple punch biopsies, as a method of treatment. Again this technique was not strongly supported by any of the overseas authorities. The amount of tissue taken is so small, and the site from which it is to be taken so difficult to identify, that even a multiple punch biopsy cannot be used with confidence.

Management by punch biopsy

The SMS Minutes record that punch biopsy specimens were to be taken, but in the body of the 1966 Proposal Dr Green says, "Four have been **treated** by punch biopsy alone" (my emphasis). As punch biopsy is primarily a form of diagnosis and only fortuitously treatment, the use of the word 'treated' is misleading.

I am satisfied that Dr Green did not intend to use punch biopsy as a method of treatment in the context of the 1966 Proposal. In my view he intended to monitor patients with positive cytology, disturbing the lesion only by the most minimal diagnostic technique – a punch biopsy.

The use of colposcopically-directed punch or wedge biopsy alone

The 1966 Proposal presented brief details of 503 cases of cervical carcinoma in situ. Four of those were said to have been **treated** by punch biopsy alone. In a paper published in the same year titled 'Pregnancy Following Cervical Carcinoma in Situ'[1]. Dr Green referred

again to those "4 patients seen in 1965 [who have had] no further **treatment** since the clinical colposcopic and punch biopsy **diagnosis** of the lesion" (my emphasis).

Three years later, in his 1969 paper, 'Invasive Potentiality of Cervical Carcinoma in Situ',[2] Dr Green referred to 16 patients whose only management by the end of 1966 was a punch biopsy to establish a histologic diagnosis of CIS and who thereafter were not offered any treatment.

By 1970 when he published 'Cervical Carcinoma in Situ',[3] the number of patients "diagnosed and treated by punch biopsy alone" had increased to 27. The same group of 27 patients was referred to again in Dr Green's 1970 paper co-authored with Dr Donovan and entitled 'The Natural History of Cervical Carcinoma in Situ'.[4] In that paper, Dr Green noted that 22 of the 27 patients had had continuing positive smears.

The number of patients for whom primary treatment was biopsy alone had increased to 99 by the time Dr Green's last paper on the topic was published in 1974.[5]

In that paper, primary treatment was defined as "that treatment status in existence one year after the date of the original (histological) diagnosis". It is clear, particularly from reading the 1974 paper, that many patients who started with punch biopsy then went on after a delay to have other treatments. Only a minority of the women who initially received punch biopsy as their sole form of treatment for CIS received no further treatment.

The fate of the minority of patients who received colposcopically-directed punch or wedge biopsy alone was discussed in 'The Invasive Potential of Carcinoma in Situ of the Cervix'.[6] In all 25 cases, excision was histologically incomplete. In other words there was no proof the punch biopsy had removed the entire lesion.

The authors categorised these 25 cases into two groups. Fifteen were placed in a Group 1 category as their follow-up smears were normal. Only one of these 15 women who had had normal follow-up cytology subsequently developed invasive cancer. The remaining 10 cases had positive follow-up cytology and were placed into a Group 2 category. Nine out of these 10 women subsequently developed invasive cancer.

Confusion over terminology

a) Treatment or diagnosis

It will be noted that Dr Green used the terms 'treatment' and 'diagnosis' almost interchangeably when writing of this series of patients. However, there seems little doubt that he intended to take only a small piece of tissue, which would be enough to establish that the woman suffered from CIS while leaving as much of the lesion undisturbed as possible, so that its future pattern and behaviour could be studied. He 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 NWH by means of 2 series of cases.
>
> "(I) A group of 27 women (up to December 1967) are being followed, without 'treatment', by clinical, colposcopic, and cytologic examinations after an initial histological diagnosis of carcinoma in situ has been established by punch biopsy of a colposcopically-significant area on the cervix. The criteria for selection of this series are: (i) the only abnormality at presentation is a positive smear. (ii) there are no symptoms possibly referable to invasive cancer (especially intermenstrual or post-coital bleeding). (iii) there is no frank bleeding on probing the endocervical canal of a normal-appearing cervix. (iv) there is no cervical area colposcopically-suggestive of invasive cancer.
>
> (v) the colposcopically-significant area is large enough not to be completely excised by the diagnostic punch biopsy.

"(II) A group of 5 women who have had a hysterectomy (4 for cervical carcinoma in situ) and who now have histologically-proven vaginal carcinoma in situ, has been accumulated.

"All have had persistent histological and cytological evidence of vaginal carcinoma in situ for periods ranging between 3 and 9 years (to March 1969) without treatment and a first report on them has been presented (McIndoe and Green, 1969)."[7]

b) Special series

The 1966 Proposal comprised a group of patients who shared a common diagnosis of CIS. Dr Green used the term "special series" in his published papers to define this group. He conceded that he did not intend to imply any design or overall control of what went on. He explained that "special series" had a particular meaning in a medical context which might be difficult to grasp. He defined this as:

"A separate group where the pathologist said this, or I said this or that, and it was decided to do this, and the information followed was that. It is fortuitous. It isn't a group set out now that we will say, 'We will do this and nothing else to this group, because they are a special series.' It just happens that most of them arrived fortuitously."

Summary and conclusions: The overseas authorities were generally agreed that punch biopsy has never, during the relevant time, been considered appropriate treatment for carcinoma in situ. Professor Richart and Dr Jordan both stated that managing patients by punch biopsy alone when they continued to have positive smears, did not constitute adequate treatment. I accept their evidence. Dr Jordan referred to Dr Green's 1974 paper which mentioned the development of invasive cancer in patients who were part of the 1966 Proposal. Dr Jordan said:

"Two of these deserve special mention.
1. Patient Code 9R had a punch biopsy which showed carcinoma in situ. This was followed by positive cytology and when a cone biopsy was performed in 1971, she was found to have invasive carcinoma.
2. Patient Code 4X had a punch biopsy in 1969, had positive cytology for the next three years, and was found to have invasive carcinoma on cone biopsy.

"Two possible conclusions can be drawn from these two cases. First, that the initial punch biopsy, in removing a portion of carcinoma in situ, reflected accurately the underlying condition, but left residual carcinoma in situ which then progressed to invasive carcinoma.

"Second, that the original punch biopsy failed to diagnose the presence of occult invasive carcinoma which continued to grow. In other words, either carcinoma in situ progressed to invasive carcinoma over the three-year study period, or alternatively the punch biopsy had failed to diagnose occult invasive carcinoma."

Dr Jordan was asked about these two patients in cross-examination:

Question: *Would you accept in either case whichever conclusion is correct, the patients in question were inadequately treated?*

Jordan: *Yes, the patients in fact were not treated. I think that is the point, not even inadequately. They weren't treated.*

The outcome for the 25 women who were included in the punch biopsy "special series" was clearly summarised in the 1984 McIndoe paper. Nine out of the 10 women who were monitored with continuing positive smears developed invasive cancer.

MULTIPLE CONE BIOPSIES

It has not been uncommon throughout this Inquiry for the term 'cone biopsy' to be used to describe both the diagnostic technique and the treatment of CIS. Professor Kolstad said that he prefers to use the term 'conization' when the technique is used for therapeutic (treatment) purposes and retain 'cone biopsy' for the diagnostic technique. This terminology reduces the confusion considerably. In either case, the intent should be to remove the entire lesion.

The 1966 Proposal did not specify that a cone biopsy was to be performed for diagnosis or a conization for treatment. Instead, during the course of the discussion at the Senior Medical Staff meeting on 20 June 1966, Dr Green confirmed that "if at any stage concern was felt for the safety of a patient, a cone biopsy would be performed".

A review of the patients' notes demonstrates that many women with continuing positive cytology have had more than one cone or ring biopsy and in some cases up to six, albeit with decreasing effectiveness. It was obvious from Dr Green's evidence that he queried the need for hysterectomy in the treatment of CIS. He believed that the mortality (deaths) and morbidity (serious consequences of the operation) associated with hysterectomy were such that less radical procedures were more appropriate. Furthermore, he believed that cone biopsy would not interfere with the woman's ability to bear children. Nor did he consider that it would increase the chances of haemorrhage. He agreed that repeated cone biopsies could tend to increase the chances of stenosis (narrowing of the cervical canal), but that such a problem was very easy to overcome. He agreed that it would be exceptional to perform five or six cone biopsies on an individual patient and could not recall any instance where he had done this.

Many of the overseas authorities and New Zealand gynaecologists commented on the practice of multiple cone biopsies. In Dr Jordan's experience it was not unusual for gynaecologists working in major colposcopy units to perform a second cone biopsy; but the circumstances would have to be exceptional for a third to be considered. He could recall performing a third cone biopsy on only two patients in the 21 years he had been engaged in this work. In his view the physical morbidity attached to cone biopsy can involve a primary haemorrhage rate requiring transfusion in 4 per cent to 6 per cent of cases.

Dr Pixley agreed that more than two cone biopsies would be an extremely rare event. He said that multiple biopsies would be extremely difficult and each of the procedures would therefore present increasing problems.

Professor Kolstad told me that if the first cone biopsy or conization was relatively high in the endocervix then it was extremely difficult to perform a second. After the second cone, if the lesion had still not been removed (that is, there was evidence of incomplete excision), then he would prefer to perform a hysterectomy rather than a third conization. Professor Kolstad also noted that if a cone was relatively large then there is an increased risk of abortion or premature birth.

Dr Laverty was concerned that both colposcopic and cytologic evaluation could be made more difficult in patients who have undergone conization. The scarring and stenosis which may follow multiple cone biopsies could theoretically worsen the problem because of the greater difficulty in gaining access to residual disease left in the endocervical canal.

Professor Bonham confirmed that he was aware that a few patients at National Women's Hospital had had at least three cone biopsies or conizations. Multiple conization in his view was a dangerous practice and with the third or fourth operation it probably became a greater risk than a hysterectomy.

In evidence, both Dr McIntosh and Dr Jamieson confirmed that a second cone biopsy would be performed where the results of the first biopsy could not establish whether or

not there was an invasive cancer present. I therefore inferred that each would use the technique of a second cone biopsy only for diagnostic purposes.

I have reached the conclusion that in following the criteria established by the 1966 Proposal, a cone biopsy would be performed if invasive cancer was suspected. Diagnosis, not treatment, was therefore intended.

The experiences of patients

Some of the women who have received multiple cone biopsies gave evidence. Their medical and personal experiences are worth comment.

In 1969 a 46-year-old woman (Patient Code 2D) with 11 children was admitted for examination following a 10 year history of "heavy, prolonged periods getting progressively worse". She had a low haemoglobin level.

Date	Procedure	Pathology Report
14/11/69	dilatation & curettage (D&C)	Probable CIS
16/12/69	Examination under anaesthesia (EUA) D&C, biopsies Cervix	CIS probably with microinvasion
7/71	EUA D&C Ring Biopsy	CIS (incomplete excision)
11/7/72	D&C, cone biopsy	CIS with microinvasion
10/7/73	D&C, ring biopsy	CIS
30/4/74	EUA, ring biopsy	CIS
15/2/77	EUA, curettage D&C	Carcinoma ?in situ ?Invasive of the cervix (endocervical curettings; sections show fragments of carcinoma that is at least in situ and possibly invasive, a further more extensive biopsy may allow a more precise diagnosis.
29/3/77	EUA, cone biopsy	carcinoma in situ excision complete
	Eight anaesthetics were administered.	

This woman was one of those who accepted without question the repeated examinations and biopsies:

> *"Well, they did find some little thing there to do with cancer of the womb.... Actually I never, ever had a discussion on anything they were going to do. I was just sent in and they just said it was exploratory tests."*

As she had had a tubal ligation some years prior to her first admission to National Women's Hospital, it seems possible that she considered her family complete and that hysterectomy might have been considered. Neither her notes nor her interview with me suggest that the topic was raised. She told me she still returns for regular checks. She finds this reassuring. She said in answer to the question:

> *"...you were told that you had cancer of the womb. Has that been talked about since that first occasion when you went?"*
>
> **Answer:** *No it wasn't talked about at all actually.*

Question: *So why do you understand you go back to the Hospital for your annual checks now?*

Answer: *I just like to go. I think they are keeping an eye on me I guess.*

Question: *Everything is fine now. Is that right?*

Answer: *Well I assume it is, they would let me know .... I have always just left it to the doctors. There are a lot that have hysterectomies and they get perhaps a bit more* [information].

This patient's knowledge of the nature of her condition and her treatment was extremely limited.

Patient Code 4M. This woman had four children and was 30 when she was first admitted in 1970 with abnormal smears. From 1970 to 1983, six biopsies described variously as wedge, ring, cone or surface biopsy were performed. On two occasions, excision was recorded as histologically incomplete.

The woman's notes comment on her wish to have more children. Before coming to meet me, she had obtained and read her file. She told me that in 1977 when a Grade 5 smear had been reported, her family was complete and she should have been offered a hysterectomy. She had been using contraception consistently since 1973 when a Dalkon Shield had been inserted. She was asked:

"You went into National Women's for smears and biopsies from 1970 to 1983 and I see from a summary on your clinical notes that you had a total of 38 visits and six biopsies during that period. How did you feel about going back to the Hospital frequently like that?"

Answer: *Well I didn't mind the clinic because I felt they would check, but frequent biopsies, six in total, were a little bit difficult because of having a young family and no family to look after the children. It was a little bit inconvenient.*

Question: *Did you ever discuss that inconvenience with any of the medical staff?*

Answer: *No...* [it was] *my lot.*

'Ruth'

'Ruth', the woman whose medical history and experiences over a period of 21 years of visits to NWH were described in the magazine article,[8] also had repeated biopsies. She visited the Consultation Clinic over 40 times before she was discharged to the care of her general practitioner. In 1965, at the start of that period, a punch biopsy disclosed a diagnosis of carcinoma in situ of the cervix. Over the next five years she visited the clinic on 14 occasions when smear tests or colposcopic examination took place. The smear tests all reported "cells suggestive of", "strongly suggestive of", or "conclusive for" malignancy.

In 1970 selective biopsies were performed and a histologic diagnosis was made of CIS with microinvasion of the cervix. 'Ruth' returned to the clinic on three further occasions when smear tests reported "cells strongly suggestive of" or "conclusive for" malignancy. She underwent a cone biopsy in 1971. The histological report was "carcinoma in situ with microinvasion of the cervix" and "hyperplastic hormone endometrium". In the same year, following a colposcopic examination, Dr McIndoe wrote:

"I would be more satisfied clinically and scientifically since this should be possible quite safely and readily to remove this small area which remains and extends onto the vagina. To come in to have this area excised in the next few weeks."

Dr McIndoe then performed a wedge biopsy and uterine curettage which confirmed hyperplastic hormone endometrium and carcinoma in situ of the cervix. 'Ruth' continued to attend the clinic and receive abnormal smear reports until 1976 when a ring biopsy and dilatation and curettage were performed. The pathology report noted:

> "Curettings:
> Sections show fragments of endocervical tissue and a few portions of **carcinoma insitu of cervix without stroma.**
> **Biopsy cervix opened at 3 o'clock;** Sections show carcinoma insitu of cervix. The tumour reaches the upper cut edge in several slides.
> **Carcinoma insitu of cervix** – excision appears incomplete."

Between April 1976 and March 1977 there were three normal smear reports. By now, 'Ruth' was suffering the consequences of repeated biopsies. The notes say:

> "LMP [last menstrual period] was somewhat painful, something that she has been unaccustomed to for many years. On examination the explanation is fairly obvious – the vaginal cervix has now almost disappeared and the external os [opening of the cervical canal] is so narrowed as to be very difficult to pick up. A No.2 dilator could not be introduced. If there is any further trouble with the next period, she may need admission for a dilatation, otherwise see in December."

Eight months later, the notes say:

> "The cervix is very stenosed [narrowed or constricted] in fact, hardly visible and she is having some dysmenorrhoea [painful menstruation]. To be admitted for dilatation...."

Following an examination under anaesthetic and dilatation of the cervix, scanty curettings were obtained. The pathology report stated:

> "...fragments of carcinoma devoid of underlying stroma, probably carcinoma in situ."

Five months later, on her return to the clinic, Dr Green noted:

> "The cervix is still somewhat stenosed but looks rather better [than] previously. The histological report is somewhat surprising. Smear taken, see in one year."

On that occasion and September 1979, the smear reports were normal. She was discharged to her general practitioner with a letter stating:

> "I understand this patient is now attending you and that you are unaware of the reasons why we have been seeing her at this hospital.
>
> "She was originally admitted in 1965 with a positive smear following a miscarriage. A cone biopsy showed carcinoma in situ. She continued to have doubtful and positive smears and she also had a normal pregnancy during.... The cervical smears continue to be doubtful or positive despite normal clinical appearances and no symptoms. Further biopsy in 1970 revealed persistent carcinoma in situ. This continued on and off until 1976, also in the absence of clinical findings or any abnormal symptoms. She had another ring biopsy in 1976, following this, the smears have been negative. There was some stenosis of the cervix which was causing her dysmenorrhoea and this was dilated in April 1977.
>
> "Today the cervix is still somewhat stenosed and she has skipped a period or two recently, but has no symptoms of dysmenorrhoea or retained menses. I do not think she needs to attend clinic for any further follow-up as she has no more chance than the next person of now developing any carcinoma of the cervix. It is possible that the cervical stenosis might give rise to problems and if she complains of abdominal cramps associated with scanty periods, this

> would be an indication for further dilatation of the cervix. I suggested that she discontinue the oral contraceptives she has been on to see if this has any effect on her scanty periods."

Her general practitioner, Dr A, did not perform any smear tests until 1985. In October of that year she was readmitted to NWH for treatment of invasive cancer of the cervix, Stage 1B.

'Ruth' was subjected to 14 years of regular monitoring at National Women's Hospital, repeated colposcopic examinations and four procedures under anaesthetic before being discharged from the clinic to the care of her general practitioner who was not told to ensure she had regular follow-up examinations. The first diagnosis of microinvasive disease was reported 15 years before she was ultimately admitted and treated for what was by this time invasive cancer. The consequences of the procedures were obvious. The constriction of the cervix not only prevented reliable smear tests being taken, but also caused painful menstruation.

Summary and conclusions: In some patients the practice of multiple cone biopsies or conizations resulted in unpleasant and painful side effects. The technique must be performed under anaesthetic. Haemorrhaging can occur, as can stenosis which causes difficulty in future colposcopic or cytologic examinations. Stenosis also created difficulties for some patients when menstruating.

A consensus of New Zealand and international opinion held that performing more than two cone biopsies or conizations is extremely rare and the risks may well outweigh the benefits of avoiding hysterectomy. In any event, there is a possibility of increased difficulty in bearing children if conization or cone biopsy has been performed. Therefore, there seemed little to be gained in repeatedly subjecting women to this procedure.

CONSERVATION OF THE UTERUS

While there were certainly occasions when patients mentioned to me that they had not wished to undergo a hysterectomy, from time to time I was left with the impression that the options and repercussions of their decision had not been fully explained to them.

Moreover, on examining patient files, I found many occasions when the possibility of a hysterectomy might have been welcomed by a patient with persisting disease, with unpleasant symptoms that a hysterectomy might reduce, and whose family was complete. For some women, repeated visits to the hospital might also have been avoided.

One woman with 16 children, Patient Code 10U, was admitted to National Women's Hospital in 1970 aged 45, with an A5 smear and a report of post-coital bleeding. A cone biopsy showed carcinoma in situ with microinvasion. The following year, her seventeenth pregnancy occurred. The notes say:

> "This patient was seen at the antenatal clinic today. It appears that she has a carcinoma in situ with microinvasion, although the significance of this is not clear.... The possibility of tubal ligation was suggested to this patient.... Prof. Bonham."

This procedure was performed and combined with an exploration of the uterus. In March 1972, on a follow-up visit to the clinic, the smear report was "cells strongly suggestive of malignancy". Two further identical smear tests were reported but in 1973 the notes record:

> "Patient rang to say she is unable to come to clinic or see her own doctor at present, owing to financial difficulties. Will contact us later when her 'financial position' is more stable."

There is a record of correspondence from the hospital to the patient and her general practitioner until 1981 when she returned reporting abnormal vaginal bleeding – "STAGE 2B Adv." (advanced) cancer was diagnosed.

In 1968, Patient Code 6W, a 35-year-old woman with six children, was first examined at the Hospital, after a positive smear. A cone biopsy performed at a hospital in Northland in 1965 had revealed carcinoma in situ. Two smear tests at National Women's Hospital in 1969 showed "cells strongly suggestive of malignancy"; and in 1970 the notes record "on pill since 1968".

A further biopsy was performed at NWH and in May 1970 CIS was confirmed in the pathology report. In 1971 another cone biopsy was performed and after her discharge from the clinic in 1972 Dr Green received a letter from her general practitioner in Auckland asking for some information on the last biopsy. In reply, Dr Green said:

> "Following the original diagnosis in May 1970 of carcinoma in situ, she had positive smears. A cone biopsy was performed on 28/9/71 during my absence abroad, this showed carcinoma in situ also. I would not be concerned about this – invasive carcinoma having been ruled out by the further cone biopsy and endocervical curettage. Her chances of developing invasive cancer are in my experience, negligible. I think she should be checked once a year for the next few years and for this reason I would be very glad to see her again if you can persuade her to come down sometime."

For the next six years her general practitioner returned the National Women's Hospital standard cancer follow-up form marked, "Alive and well, without evidence of cancer." In 1978, however, she was readmitted to NWH, received a diagnosis of "Stage 3AB Cervix" (cancer) and died just over one year later. Her notes disclose no indication of a discussion about hysterectomy.

In 1961 Patient Code 6U, a 39-year-old woman with three children, was admitted after two months of irregular P.V. (vaginal) bleeding. She had been sterilised about seven years earlier. The pathology report on her cone biopsy stated:

> "Atypical dysplasia and undifferentiated carcinoma of cervix. The lesion is predominantly in situ, but at one point the appearances suggest early micro invasion. The lesions extend to the cut edges of some sections. No emboli seen."

(When the pathologist examined the tissue sample he could see evidence of disease at the cut edge. This meant it was possible that part of the lesion remained behind in the cervix.)

After three follow-up negative smears, a positive smear was reported and a further cone biopsy performed two years after her initial admission. From that point on the woman attended clinic on many, many occasions. Two and a half years after her first admission, her notes disclose that she was being treated for anaemia. The smear tests were from time to time normal, but more often positive or equivocal. Clinical signs and symptoms indicated invasion. Later she began complaining of painful periods and by 1969, following colposcopy, Dr McIndoe noted:

> "...however, there is quite a clear three dimensional lesion, particularly in the upper third of the vagina but also extending down in a patchy way almost to the junction with the mid and lower third of the vagina. The degree of this lesion varies from area to area, but I am quite convinced today that the appearances are for real...."

Subsequently, "continuous vaginal bleeding" (for about six weeks) was noted. By October 1970 the notes state:

> "...I think probably in view of the persistent menorrhagia and endometrial histology (hyperplasia) that hysterectomy is probably indicated, but this is of less immediate importance than her chronic renal disease, due to the neurogenic bladder...."

On her next visit, six months later, the notes state:

> "...however, she is not keen to have hysterectomy with the improvement in her periods. I have postponed this meantime...."

There is every reason for me to suspect that she did not know that her smear tests and clinical signs were indicative of continuing disease. In 1969 the notes state:

> "Seen by Dr C privately and was surprised to get a positive smear. Colposcopy by Dr McIndoe this morning."

A smear taken at NWH just two months earlier, had been "cells conclusive for malignancy" and the smear taken during the colposcopic examination reported "cells strongly suggestive of malignancy".

Towards the end of 1971 Dr McIndoe noted:

> "She should come in urgently for a D&C and whilst in, the opportunity should be taken for further biopsy of the cervix. I would wonder whether hysterectomy may not have been considered in the foreseeable future."

When a cone biopsy was taken the clinician performing it said:

> "No evidence of invasive carcinoma of cervix",

however, the pathology report on the cone biopsy stated:

> "Sections show a lesion which is at the least, carcinoma in situ. The appearances suggest an active progressing lesion. The appearances of one relatively large tumour mass may suggest that there could be invasive carcinoma nearby, probably at the endocervical area. In any case, tumour is present at both portio and excision margins. If there should be sufficient indications later, a further cone biopsy to incorporate more of the endocervical canal may be worthwhile. Carcinoma-in-situ of the cervix ?invasive carcinoma nearby."

Six weeks later the woman returned

> "in great distress and pain because of pain in her back and apparent stimuli of the sciatic nerve in various positions, she is extremely careful and even talks of suicide the pain at night is so bad. She has had a fairly heavy period since 8th December but this has now almost ceased. Cervix looks absolutely normal but there was some bleeding on probing the endo cervix, presumably menstrual blood. I should think that positive cervical cytology and the report of carcinoma in situ are the least of her troubles..."

This woman continued to visit National Women's Hospital on innumerable occasions, receiving many examinations and biopsies. Her smears were consistently positive. Clinical examinations and biopsy results confirmed persisting disease. In December 1978, following an examination under anaesthetic (EUA) and curettage of the vaginal vault and biopsy of the cervix, the notes state:

> "It looks like ulcerative, invasive cancer, but she certainly has no symptoms.... It seems to be the concensus that radiation was not justified unless there was definite histological diagnosis of invasive cancer. The other suggested treatment was total hysterectomy and vaginectomy (Mr W) possibly this could be regarded as even more radical than radiation at the present stage, especially in an asymptomatic patient."

Following radiation therapy, the notes report "looks the picture of health...the vaginal vault is obliterated and the cervix no longer visible". By November 1981 it seems that this patient was advised that there was no further treatment available for her disease and when she died in the Hospital 10 months later it was her 65th visit to NWH. By that date she had had at least 50 vaginal examinations and 24 more major procedures, 12 of them under general anaesthetic.

Summary and conclusions: I accept that hysterectomy is an operative procedure which some women may wish to avoid. However, in the instances I have cited it is clear that the patients themselves did not wish to have any further children and their disease was such

that the possibility of a hysterectomy should have been seriously considered and discussed. Other symptoms might have been ameliorated by the procedure and possibly the number of examinations and procedures under anaesthetic reduced dramatically.

THE SAFEGUARDS

Dr Green and his colleagues who approved the 1966 Proposal spoke of the safeguards which were in place and which were expected to protect the patients in the study. They included:

- Dr Green's expertise
- exclusion from the trial of those women diagnosed with invasive carcinoma
- colposcopic examination to ensure there was no significant abnormality of the cervix
- cone biopsy if invasive disease was suspected or detected
- only women under the age of 35 were eligible for inclusion in the trial
- patients were to be closely monitored
- and there were to be no clinical signs of invasive carcinoma.

Were the safeguards observed?

During the course of the Inquiry the notes of 24 women who had been included in the Proposal and had died from a variety of causes were reviewed to consider how far these safeguards had protected them. With three exceptions, all women were over 35 years of age. This 'safeguard', therefore, had largely been ignored.

The notes of patients disclosed that not only were women over the age of 35 with positive smears included in the 1966 Proposal, but laboratory and clinical evidence suggesting the possibility of invasive cancer was overlooked or downplayed and warnings of progressive disease were dismissed or ignored. As those whose specialist participation was essential to the safe conduct of this Proposal became more estranged, the criteria were followed less and less rigorously.

There were symptoms (for example abnormal bleeding) indicative of possible invasive cancer referred to in the notes of a large number of these 24 women. An earlier diagnosis of microinvasion can also be seen in many of the notes. Bearing in mind the criteria for inclusion in the 1966 Proposal, it would seem that these women should never have been included, or should have been removed at an earlier stage. (A synopsis of their ages, the signs that the 'safeguards' were not observed, the period after admission when invasive disease was diagnosed, and the date and cause of death can be found in Appendix 12.)

Follow-up of patients

National Women's Hospital has for the past 30 years adopted a policy of assiduous and thorough follow-up of patients diagnosed with CIS. For some time hardly a patient was misplaced. Dr Green himself wrote to patients on occasions and took great pains to enquire about their health and families and to reassure them. Miss Owen, who in 1987 was working part-time at the clinic, has given superb service to the Hospital over many years. Her care and ingenuity in locating patients, unaided by computerised facilities, deserves the warmest praise as does her unfailing courtesy and willingness to help locate files for my medical advisers and Inquiry staff.

Nevertheless, follow-up, however well done, did not always result in treatment. Indeed, I have come to the view that Dr Green's care in this part of the Hospital's work resulted from his need to keep track of the condition of patients with positive cytology who were part of his 1966 study. Great efforts were made to locate patients throughout New Zealand and even after they had moved overseas.

In one example, the follow-up of a woman with positive cytology (Patient Code 1X), the

first recorded smear test is reported as A2 (Grade 2). There was a histological diagnosis of carcinoma in situ of the cervix. In 1967, after an A2R (Grade 2R) smear, her notes say, "Follow-up Ca-In-situ – punch biopsy only...." Three further equivocal or positive smears were reported until she was referred to a gynaecologist in Wellington. Dr Green wrote to him:

> "This patient is one of my 75 with positive smears about whom I spoke at the Post-graduate course.... As you know, I would not be too worried about the A4 smear providing she has no symptoms, no bleeding on instrumenting the endocervix and the colposcopic findings do not suggest further investigation. You will understand that she is a fairly important case and I will be interested to hear what you decide to do with her."

The woman herself had been told in a letter,

> "As you know, you have the condition which many people have thought in the past might go on to a true cancer but which we have now realised in this Hospital is not so. Gynaecologists generally, outside Auckland, without the facilities of National Women's Hospital are naturally inclined to view this condition more radically than we do here and so I warn you that any specialists that you go to may suggest further surgery is necessary."

He then went on to recommend that she consult Dr Duncan who examined her from time to time and reported back to National Women's Hospital. On one occasion he reported a histological diagnosis of CIS and said, "I will continue to observe her as in the past", earning this commendation from Dr Green, "I am glad of your reports and the conservative attitude to this disease that they display."

In 1971 Dr McIndoe wrote to Dr Duncan while Dr Green was absent overseas, urging that an in-patient biopsy be performed if it had not already been done. He said:

> "Professor Green aims at an adequate biopsy of any abnormal areas but does not attempt to remove the area completely. My own tendency is to excise such abnormal epithelium as I can demonstrate, but as conservatively as possible."

Dr Duncan wrote back to Dr McIndoe saying that he was starting to get

> "a little touch of the cold feet as to whether I should remove rather more of this lesion. However I am prepared to wait a little longer and I am very much Herb's servant in this one as I promised to do what he wanted."

Not surprisingly Dr Duncan was asked about this exchange of correspondence. He told me that he had assumed that the 1966 Proposal had been a properly controlled and authorised trial. Under those circumstances he was more than willing to fit in with its protocol. It was on that understanding that he undertook the care of this patient. However, he began to become concerned at the possibility that this woman's condition was not fully canvassed by adequate biopsy. As a result he admitted her and following biopsy obtained a histopathological report confirming a small area of in situ carcinoma. Furthermore, he was taking pains to keep the woman herself fully informed of the mode of management.

Dr Duncan said that in 1969 he was starting to move from performing only cone biopsies for treatment of CIS to local destructive methods with the assistance of colposcopy. He told me that the method of management requested by Dr Green was "very much contrary to my personal philosophy" and further

> *"I don't think I would have in fact been able to allow her to go on any longer than my colleague in Christchurch did, in all conscience, thinking about this one."*

He was asked whether he was treating the patient in this manner because he was acting on the basis of a research programme and "in effect carrying that out under limited horizons"?

Answer: *"Yes... I would certainly say that quite emphatically because we were*

given the impression that this was one of the big projects they wanted to do and that everybody was fully aware of what was happening.... We would do the same now about somebody who was in the process of being followed up on some other topic. I don't think in this particular area of course, [monitoring the natural history of CIS] *because of what is widely known now....*

"If a person is prepared to get up at a large meeting and discuss the management of his cases which has been done on a prospective programme for many years...this would never have got under way unless it had been okayed by ethical committees.... In those days I think we were still entitled to assume that this was an agreed department programme."

In 1972 the patient moved from Wellington and was again referred to a gynaecologist whom Dr Green felt would not recommend a hysterectomy. Dr Green wrote to Dr Duncan:

> "...but she may be lucky if she gets away from Christchurch intact. I think [gynaecologist's name] would be the best person to refer her to, at least I know him well enough to reproach him if he wants to do a hysterectomy."

The Christchurch gynaecologist reported examining this patient and noted that the "cervix bled easily to the touch". Among other comments in his letter to NWH, he said:

> "I note her history of carcinoma in situ which you seem determined to treat in a fairly cavalier manner."

These notes demonstrate the extent of Dr Green's zeal which, on this occasion, led him to attempt to continue to control a patient's treatment from a distance. Information of this type leads me to the conclusion that follow-up was not conducted for the purpose of monitoring and treating the patient where necessary, but to ensure that no data were lost which could be included in the study results.

Follow-up also had extreme consequences for a great number of the women from many parts of Auckland and Northland who attended clinic at least annually and often more frequently. Significant numbers of these women were mothers of young children. Most women were inconvenienced by constant return visits. The knowledge that they were being monitored and not treated will increase any feelings of frustration and anxiety.

Diagnosis of invasive cancer

The most critical safeguard for the patients included in the 1966 Proposal was Dr Green's belief that with clinical and colposcopic examination and no symptoms of invasive disease, he could confidently allow women with positive smears to continue without treatment. The safety of his study depended on the clinician's or colposcopist's ability to state reliably:

a) that a woman did not suffer from invasive disease when she was included in the trial
b) that if invasion did occur, she would come to no harm.

But given the nature of this disease, once invasive cancer is diagnosed, her treatment is more radical and her life expectancy significantly endangered.

I do not consider that he was justified in his confidence that the possibility of invasive cancer could be excluded at the time that a patient was enrolled in the study. Even in his 1967 paper, 'Is Cervical Carcinoma in Situ a Significant Lesion'[9] Dr Green wrote of four women in the special who were being monitored by punch biopsy alone. He said:

> "With the possible exception of four cases in the special series referred to above, invasive cancer has been excluded as far as possible from the outset."

Therefore he was already aware of the possibility that invasive cancer might not have been detected.

I am satisfied that the failure to detect invasive cancer was in large part due to the fact that the punch biopsy was inadequate as a means of diagnosis. Today an expert colposcopist

might have the skills and knowledge which enable him to punch biopsy the most appropriate area of the cervix and confidently make a diagnosis concerning the presence or absence of invasive cancer. In 1966 Dr McIndoe did not. Indeed, very few clinicians in the world at that time could have used colposcopy and punch biopsy as a means of excluding invasive disease. This was especially difficult in women over 35, where the whole abnormal area on the cervix is less likely to be visible.

Quite apart from these difficulties, obvious symptoms of invasive disease were sometimes overlooked or downplayed. Within a fairly short time the risks became apparent. As early as 1967 the dangers of the 1966 Proposal in terms of missed and therefore delayed diagnosis of invasive disease should have been evident.

In 1967 a 77-year-old woman (Patient Code 6G) was admitted to NWH with a reported A4 smear and six days of postmenopausal bleeding. The pathology report following a ring biopsy disclosed

> "carcinoma in situ with microinvasion of the cervix – ? invasive carcinoma nearby. Curettings: Sections show hyperplastic cystic endometrium."

Following a review of the notes one month later, Dr Green wrote:

> "Follow-up carcinoma in situ with micro-invasion – See somewhat unusual pathology report 'the character of the edge of a truly invasive carcinoma, the bulk of which is still in the cervix'. The patient has no symptoms and the cervix is healed perfectly, leaving a completely normal atrophic cervix. If it were an invasive cancer, the bulk of which is still in the cervix, one would have expected something more obvious by now. There has been no bleeding or discharge since six days following the cone biopsy. Smear taken, see in 4 months."

Four months later the notes report:

> "Cervix is unchanged from previous examination. No symptoms. See again in 4 months."

The smear test reported:

> "cells conclusive for malignancy. We feel cytologically there is a significant chance this lesion has progressed beyond the insitu stage."

The patient was readmitted, a cone biopsy performed and occult immature mixed (invasive) carcinoma of the cervix diagnosed.

By the end of 1969 three cases of invasive disease had occurred in patients who had been monitored for more than a year with continuing positive cytology. The inference should have been drawn that following patients with persistent CIS was unsafe. Even if Dr Green could not accept that in some cases CIS was shown to be a premalignant disease, then his alternate explanation that the presence of invasive cancer had been missed at the outset when the women were first included in the group shows that the Proposal was incapable of testing his hypothesis. Therefore it was scientifically unsound and dangerous to the patient.

The consequences for the patients whose invasive disease was not diagnosed before they were included, or who had symptoms or histology reports that were subsequently overlooked are extremely serious. For example, 'Ruth' was discharged from the care of the Hospital Consultation Clinic after five 'normal' smears. Professor Kolstad was extremely critical of the reliance on these smears. He said:

> *"A smear which does not contain columnar cells which shows that you have a smear which is representative for the cervical canal, if you don't have that, then the smear is indecisive. We always in our reports, we mention this in the report, that we have no signs of malignancies, but we don't find any columnar cells which means that you report back to the doctor taking that smear that he has not managed to get a specimen from the endocervix.*
>
> *"And then Professor Green in April once more did a dilatation of the cervix*

and curettage and here once more 'fragments of carcinoma – devoid of underlying stroma. Probably carcinoma in situ'. You don't know that.

"It might be an invasive cancer because you have no stroma.... The third paragraph 'I do not think she needs to attend clinic for further follow-up as she has no more chance than the next person of now developing any carcinoma of the cervix' [letter to her general practitioner], *that is, I think this is, he has misunderstood what he really found and the grades, and the smears Grade I that Mr Collins talked so much about yesterday, they can be explained by the stenosis and there were no signs I would think of columnar cells in that so it was not representative for the endocervix. Thank you.... She should not have been discharged. She should have been followed up very carefully; and she developed invasive cancer of course."*

Carcinoma in situ is a condition which has been described as almost 100 per cent curable. Invasive cancer is far more difficult to treat and cure and becomes increasingly difficult as the disease progresses.

Summary and conclusions: An analysis of the data as it began to emerge during the Proposal would have demonstrated clearly that the belief that CIS rarely if ever progressed to invasive disease was quite wrong. The graph in Appendix 3, Table 4, displays the dramatic rise in the number of invasive cancers diagnosed within 10 years of an original diagnosis of CIS during the period that the 1966 Proposal was in operation.

THE COST OF THE 1966 PROPOSAL

It is obvious that in human terms, a sizeable group of women who were included in the 1966 Proposal paid the cost of innumerable visits to the Hospital, frequent procedures, deteriorating health and great inconvenience to themselves and their families. The financial cost to the Hospital and therefore the public is also a factor. If these women had been treated definitively and by generally accepted standards at an early stage in their disease, then the cost of repeated clinic visits and operative procedures might have been significantly reduced and other women seen in their place. There is also the enormous if unquantifiable cost involved in accumulating data over such a lengthy period. The costs also include specialist, nursing, administrative and clerical time, as well as the hidden costs of additional in-patient care and the consequential pressures on hospital resources.

PUBLISHED PAPERS BY DR G H GREEN

Dr Green's published papers were studied closely during the Innquiry. Four broad topics are of relevance.

1. The outcome of conservative treatment of CIS

Papers published between 1962 and 1964 dealt principally with the outcome of conservative treatment, that is cone biopsy, and showed that this sort of local treatment was effective in curing the patient (that is, returning the patient to negative cytology) in about 80 per cent of cases.[10]

2. The invasive potential of CIS

From 1964 to 1974, Dr Green addressed the question of the invasive potential of CIS of the cervix and considered the 'clinical evidence'. This evidence was based on an examination of the outcome for patients with CIS who received different methods of management. Most patients discussed in the earlier papers had been treated by either hysterectomy or cone biopsy, with complete or incomplete removal of the abnormal area. Patients were followed up and it was found that only one woman subsequently developed invasive cancer out of 503 managed to the end of 1965. In his 1967 paper Dr Green argued that on this evidence, "carcinoma in situ of the cervix may not be a serious lesion".

From the papers published in 1966 and onwards, clinical evidence concerning this group of patients was presented in two different ways:

i) Patients were grouped according to the results of their cervical smears during the period of follow-up.

In 'Pregnancy Following Cervical Carcinoma in Situ'[1], 32 patients had positive smears following 'local excision of the lesion' – punch, ring (less than 2cm deep), or cone (more than 2cm deep) biopsy, or amputation of the cervix. By the time the 1967 paper had been published, 35 patients had been accumulated, 73 in the 1969 paper, 75 in the two 1970 papers and 96 in the 1974 paper.

The outcome among this group was discussed from time to time in Dr Green's papers. In the 1966 publication, one case of apparent progression to invasion was noted and reported as an incidence of one case in 503. Although the whole study involved 503 cases, only 32 demonstrated positive cytology after treatment. The progression rate should therefore have been reported as one case in 32. The one case is not mentioned again in subsequent publications. In the 1970 papers, again one case of progression to invasive cancer was reported. This was a different case, and one which at the outset had probably been treated adequately by generally accepted standards.

ii) Patients were grouped in a 'special series' who "have had no further treatment since the clinical, colposcopic and punch biopsy diagnosis of the lesion".

In the 1966 paper four patients are included in this group, 16 in the 1969 paper, 30 in the two 1970 papers, and 99 in 1974. By the time the 1974 paper was published, secondary treatment had in fact been offered to all but 41 of those patients. By 1970, none of the patients in the 'special series' were said to have developed invasive cancer. Dr Green's conclusion was therefore:

> "Providing invasive cancer is adequately excluded at the outset, the patient with diagnosed insitu cancer has only the normal chance of developing invasive cancer in the future."

3. Interpretation of data

By the time the 1974 paper had been written, seven and possibly 10 patients from those included in the groups studied had subsequently developed invasive cancer. Dr Green concluded that the progression rate was seven or 10 out of 750 (0.9% or 1.3%), or six out of 96 'incompletely treated lesions' (6.3%). Dr Jordan commented on this paper in his evidence. In his view a different interpretation could be placed on these figures. He said:

> *"Of the 750 cases discussed, 96 had continuing positive cytology during the follow-up period. So from this we can conclude that the remaining 654 patients were free of disease and therefore should not have been included in the study. This leaves 96 patients with continuing positive cytology in the follow-up, in whom it was assumed there was ongoing carcinoma in situ. At the time of writing the paper, 52 of these patients had not been assessed further, so it is impossible to comment on whether or not this group of 52 patients already had unsuspected invasive carcinoma.*
>
> *"We are left with only 44 patients with ongoing carcinoma in situ, who had further investigation and of these, 7 were found to have invasive carcinoma. In other words, the incidence of known progression to invasive carcinoma was 7 cases in 44. This figure approximates to that reported by McIndoe 10 years later."*

There was, therefore, a much higher proportion of invasive cancers in the patients who had been incompletely treated compared with those who had been returned to negative cytology. The incidence of cancer in the former, was at least 6.3 per cent and in the latter, four out of 652 or 0.6 per cent. Those women whose lesion had not been eradicated, as evidenced by continuing positive cytology, had at least a 10 times higher chance of developing invasive cancer than those who had been treated by generally accepted standards.

Although Dr Jordan considered that at the very latest, when the results published in the 1974 paper were known, the "trial should have been abandoned", no major revision of Dr Green's view stated in 1970 took place.

Dr Green did not interpret the results emerging from his study in the same way as Dr Jordan. He explained his results by suggesting that either invasive cancer had not been adequately excluded at the outset, or had been over-diagnosed (a lesser disease, inaccurately diagnosed as invasive cancer) at the end. Dr Green had criticised Petersen's study because, in his view, invasive cancer had not been excluded at the outset. He therefore doubted the conclusion concerning progression of the disease from CIS to invasive cancer. His own study contained a similar flaw. He too, could not confidently state that invasive cancer had been excluded when a patient was first entered in his group. His study was therefore of little scientific value in helping solve the riddle of the progression rate of carcinoma in situ to invasive cancer.

Nevertheless, one outstanding fact ought to have been clear to him and to others – following (without treating) patients with positive smears, whether after punch or cone biopsy, or after hysterectomy, was unsafe, as a proportion of those women would subsequently be shown to have invasive cancer.

It was clear that Dr Green had made errors in interpreting his own data, both on the effectiveness of cervical screening, the natural history of CIS of the cervix and the safety of following patients with positive cytology.

A further claim has been made that Dr Green did not present his data in a scientifically accurate way. Professor Richart criticised papers by Dr Green on the grounds that he had changed the inclusion criteria of the study retrospectively. He suggested that if a patient initially diagnosed as CIS was subsequently found to have invasive cancer, her initial histology was reassessed and she was, in some instances, reclassified as having invasive cancer at the outset. Professor Richart made the following comment:

> *"It is apparent from his* [Dr Green's] *description of the cases on pages 37-40 of his brief and published in his paper of 1974 that when he discovered a patient with invasive cancer who he originally had diagnosed as having only carcinoma in situ, that he retrospectively excluded the patient from the study on the assumption that the cancer had been missed when the patient was admitted to the study."*

Three things support Dr Richart's conclusion. The first was a memorandum from Dr McIndoe to Dr Green dated 15 April 1969:

> "Your raising with me on Monday 14 April of my comments concerning regrading patients originally diagnosed and classified as Carcinoma In Situ – regrading to Invasive Carcinoma and thus making them incligible for inclusion in the Ca in Situ followup series, gives me an opportunity of raising with you a number of the issues involved."

Secondly, Dr John Donovan, co-author of the 1970 paper said:

> *"All I can remember is that Professor Green told me that there had been some patients, and I think he told me that there were five of them, who had been included with this group of patients with carcinoma in situ, had developed invasive cancer, and he had looked again at the original slides and concluded they had invasive cancer in the first place."*

Thirdly, the medical review undertaken by the Inquiry's medical advisers confirmed that there were at least seven cases in whom invasive cancer was diagnosed within one year of the original diagnosis of CIS – so-called 'missed' invasions which were diagnosed prior to the publication of the 1970 paper by Green and Donovan.

4. The effectiveness of cervical screening

In Dr Green's 1964 paper and following publications, epidemiological evidence was

produced to claim that the introduction of cervical screening in New Zealand (from 1954 in Auckland) had not been effective. This epidemiological evidence put forward by Dr Green changed a little over the years. Nevertheless, it was presented right up to 1981[11] with the claim that not only was cervical screening not effective in New Zealand, but that the figures from New Zealand

> "cast doubt...on the value of cytological screening in the control of cervical cancer."

No expert witness giving evidence at the Inquiry supported the conclusions of these studies. Moreover, comment published on Dr Green's 1978 paper by G Johannesson and N E Day,[12] (leading gynaecologist and epidemiologist in this field) is worth noting:

> "In the recent article by Green, the trends in the incidence and mortality rates for cervical cancer in New Zealand have been examined in relation to the level of cytological screening. These data show that screening as practiced in New Zealand has had no appreciable effect on either morbidity or mortality. The author then claims that these data throw doubt in general on the value of cervical screening and that the significance of the 'pre-cancers' revealed by cytology and the value of population screening would seem to be doubtful. We feel that, given the data presented, this conclusion is unjustified.
>
> "Screening will have little effect on future mortality or morbidity if either:
>
> (1) Tumors grow too quickly to be more than rarely detected in a preclinical or precancerous state by screening, unless screening is repeated with an impracticable frequency; or
>
> (2) Treatment of those detected in a preclinical disease state does not appreciably improve prognosis; or
>
> (3) Screening is confined to those at low risk for disease."

The authors discuss and dismiss the first point. On the second point, they make an interesting statement:

> "The second point depends on the thoroughness of the follow-up of those detected with precancerous lesions. If these cases are poorly controlled, then progression to an advanced tumor is a considerable possibility and the effectiveness of the screening is diminished."

In other words, if patients in whom precancerous lesions are detected are not adequately treated, then little is gained in having detected the disease by screening in the first instance.

In discussing the third point, the authors suggest that the evidence produced by Dr Green is consistent with a failure to screen those at higher risk in the population, particularly, women over 35 and Maori women.

> "The conclusion one draws from negative results as reported from New Zealand is either that the wrong subgroups of the population were selected as the main target for screening, or that the high risk groups in the population have escaped screening for reason of no general applicability."

Effects of Dr Green's papers

It is difficult for me to assess just how influential Dr Green's papers have been on the understanding of the natural history of cervical cancer and on clinical practice. The evidence has shown, however, that both in New Zealand and overseas his work was known and discussed. There are two main instances where his work appears to have been influential.

1. Dr Noda, currently the Director of the Departments of Cytopathology and Gynaecology at the Osaka Cancer and Prevention Detection Centre, and Assistant Professor of the Departments of Obstetrics and Gynaecology, Osaka city and Kansai Medical University, produced in evidence a table showing studies of the natural history of CIS

to 1975. He included Dr Green's study published in 1970 showing no progression to invasion. Dr Green's 1974 publication was not referred to in this table.

More importantly, Dr Noda described his current management of patients with CIS wherein certain patients in whom invasive cancer had been excluded by colposcopy and multiple colposcopically-directed punch biopsies, and where there was no diagnostic disagreement,

> *"We consider it sufficient merely to follow-up the patient without further treatment, until such time as we observe microinvasive carcinoma."*

I have inferred that this form of management is based on an expectation of a very low chance of progression to invasion.

2. The understanding of the natural history of CIS of the cervix by staff at National Women's Hospital appeared to have been strongly influenced by Dr Green's views; in particular, a number of the staff did not accept the findings of progression in the McIndoe et al 1984 paper.[6]

Publications after 1974

In 1974 Dr Green had documented that at least 6.3 per cent of "incompletely treated" cases of CIS were subsequently diagnosed as having an invasive cancer. These patients with positive cytology had been monitored for a mean follow-up time of 3.3 to 4 years. As the natural history of CIS was already widely held to include a very long pre-invasive period, it was likely that further cases would be diagnosed.

As the 1974 publication did not indicate that the Proposal had been terminated, further information on the outcome of the study was very important. When Dr Green was asked in cross-examination why he published nothing further on the study after 1974, he said that Dr McIndoe was known to be writing up the final outcome.

PAPERS BY DR W A McINDOE, DR M R McLEAN, DR R W JONES AND P R MULLINS

The first publication by Dr McIndoe, using clinical evidence to investigate the invasive potential of CIS, was in 1969. This paper was jointly written with Dr Green and documented four cases of vaginal CIS following hysterectomy for cervical CIS. These patients were followed without treatment and none had become invasive at the time of the report.

The next publication by Dr McIndoe, using these data, was the paper 'The Invasive Potential of Carcinoma in Situ of the Cervix' by McIndoe, McLean, Jones and Mullins, published in 1984.[6] This paper presented the outcome for 1028 women who had a histological diagnosis of CIS of the cervix at National Women's Hospital from 1955 to 1976.

The patients were all followed for between five and 28 years after their initial diagnosis. In presenting the results, the authors divided the patients who had had abnormal cytology at follow-up into a subgroup in the same way that Dr Green did in his papers from 1966 to 1974. In 1974 Dr Green documented 96 such patients. By 1984 this number had increased to 131 (Group 2).

The other group consisted of patients who had normal smears two years after initial management (Group 1). Among the 817 patients who had normal cytology follow-up, 12 (1.5%) developed invasive cancer. Among the group followed with abnormal smears, that is, with evidence of persistent CIS, 29 (22%) developed invasive cancer. The authors concluded that patients in Group 2 were 25 times more likely to develop invasive cancer than patients in Group 1. In addition, 10 cases were monitored with positive smears following punch biopsy only. Nine of these cases developed invasive cancer.

The conclusions of this study have been questioned by some staff members at National Women's Hospital in their evidence before the Inquiry. The criticisms come under four broad headings.

1. The total number of patients included in the study differed from the total number on the Hospital cancer register for those years.
2. It was alleged that some patients included in the study actually had invasive cancer at the outset and were treated as such.
3. Many of the patients included in the Group 2, ie those followed with positive cytology, had already had cone biopsies or hysterectomies. Could progression be claimed in these cases?
4. The persistence of positive smears may have been a sign that the patient would develop invasive cancer, irrespective of treatment.

Because the scientific conclusions of this paper and their status were important to the Inquiry, these criticisms have been addressed in more detail.

1. The total number of cases of CIS included in the study differed from the total number on the Hospital cancer register.

The review by the Commission's medical advisers provided information on this question. The site register did not contain the names of 34 patients included among the 1028 in the McIndoe paper. Conversely, the McIndoe paper did not include 200 patients whose names were recorded on the site register. Most of the exclusions from the 1984 paper could be explained.

The site register for Stage O cancer (CIS) was found to include cases who actually had a diagnosis of CIS with microinvasion either at the outset or during follow-up. These cases were understandably excluded from the McIndoe paper. The site registers were also found to contain a number of cases where the diagnosis of CIS was made at National Women's Hospital, but where definitive treatment was carried out elsewhere.

For a small group, the reasons for exclusion were not obvious. However the Commission's medical advisers concluded that the inclusion of these unexplained cases would have been most unlikely to have altered the findings of the 1984 paper.

2. It was alleged that some patients should not have been included in the study because they had invasive cancer at the outset.

There are two parts to this criticism. First, Dr Jamieson and Dr McIntosh in their review of the paper, categorised five of the patients included in the 29 who progressed to invasion as "invasive at the outset and treated as such". The medical advisers examined the files of these cases and did not agree with this categorisation in four cases – all had an earlier diagnosis of CIS or dysplasia.

In one case, the prior diagnosis of CIS was made at another hospital (although the histology was examined at National Women's Hospital) and the patient was not seen at NWH until she had the diagnosis of invasive cancer. She was therefore included by McIndoe et al as a case with incomplete follow-up details. This case should probably have been excluded along with the cases whose definitive treatment was not at NWH.

The second criticism has been that the findings do not represent true progression to invasion among the Group 2 cases. Some of these cases may have been harbouring an invasive cancer at the outset which was not diagnosed because of an incomplete biopsy. Professor Richart commented on this problem:

> *"Most studies of the natural history of CIS of any organ suffer from the fact that one can never be sure of the diagnosis without removing the lesion and that once the lesion is removed, its natural history can no longer be studied."*

But he suggested that for cervical cancer, with the use of cytology, colposcopy and punch biopsy "invasion can be ruled out for all practical purposes in the study design" and, "most importantly, the time course of the disease will clearly sort out those patients who

have invasion at the time of admission to the study. They will rapidly become clinically apparent".

Dr McIndoe and his colleagues dealt with this problem by excluding from their analyses the eight patients who developed invasive cancer within one year of the initial biopsy. "This 12 month interval has been allowed to avoid the possibility that invasive carcinoma had been missed at the initial biopsy. This was an appropriate approach and was probably necessitated by the doubts raised about histological diagnoses from small and incomplete biopsies.

3. Could progression be said to occur after a cone biopsy?

Professor Bonham pointed out that patients were treated by cone biopsy to remove the lesion and asked, "Is it possible that the authors are contending that a removed lesion progresses!"

In fact, the paper made it clear that the majority of cone biopsies on Group 2 patients showed incomplete excision of the abnormal area (74%). By comparison, only 24 per cent of the Group 1 patients had cone biopsies showing incomplete excision. Moreover, Dr McLean suggested in cross-examination that he understood the incomplete excision to be deliberate. In most cases, therefore, the lesion was known not to be completely removed. There is the additional possibility, especially in the older patient, of a multifocal lesion being present.

4. Were persistent positive smears merely a sign that the patient would develop invasive cancer, irrespective of treatment?

In his evidence, Dr Green quoted Dr Skrabanek's then unpublished comments on the McIndoe paper:

> *"'About 20% of patients with persistent or recurrent abnormal cytology developed invasive cancer within ten years. Could this mean that those 'pre malignant' lesions which are 'cured' could never become malignant if left alone, or those truly pre-malignant are not curable by excision?'"*

Dr Green went on to say:

> *"To answer this is impossible with present knowledge and methods of diagnosis and treatment. Some research and characteristics of individual DNA strands in the cells of individual patient's cells promises some hope for a further answer to this dilemma."*

In other centres CIS was regarded as virtually 100 per cent curable. Moreover if Skrabanek's hypothesis was true, then changes in treatment practices at National Women's Hospital would have had no effect on the proportion of cases of CIS which subsequently became invasive. Skrabanek's hypothesis that there are truly premalignant lesions which are not curable by excision seems unlikely as the review showed that in the years following the adoption of the 1966 Proposal, there was a marked increase in the likelihood of subsequently developing invasive cancer.

The statement of Skrabanek's hypothesis

> "that those premalignant lesions which are cured, could never become malignant if left alone, or those truly premalignant are not curable by excision",

bears a remarkable resemblance to

> "an aphorism ascribed to Galen [which] reveals the kind of invulnerability claimed by physicians for hundreds of years: 'All who drink of this remedy recover in a short time except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases.'"[13]

A fifth possible criticism could be the categorising together of patients who had positive

smears as Group 2. It might be suggested that such a grouping of at-risk patients made the figures for rates of progression much higher. The use of the Group 2 category corresponded with Dr Green's category of patients with positive follow-up cytology. Patients had been categorised according to the likelihood that they had persistent disease. This was appropriate for the analysis of the natural history of CIS, while it would not have been appropriate for an analysis of the effectiveness of different forms of treatment.

It is also possible that these results under-estimate progression to invasion. Professor Richart maintained that most patients had biopsies of various sorts and "the biopsies reduce the amount of disease present, and may remove areas most likely to invade". Furthermore, it is possible that the results also under-estimate early regression of the lesion, as patients whose positive smears resolved within two years of their initial management were not included in Group 2.

Dr Jones in his evidence, mentioned the results of an updated analysis of the outcome of 75 patients who had been classified as cases with positive follow-up cytology by Dr Green in his 1970 paper with Dr Donovan. At that time no cases were reported as progressing to invasion. By 1987, when Dr Jones reviewed them, 47 patients had negative follow-up cytology after treatment, and 14 cases (19%) had progressed to invasive cancer.

Summary and conclusions: An analysis of Dr Green's papers points to misinterpretation or misunderstanding of some data on his part, and on occasions, manipulation of his own data. The papers have been cited and debated by various authorities over the years. It is important that the validity and influence of Dr Green's papers be viewed in the light of the information which has been placed before me. The inference to be drawn from Dr Green's 1966 Proposal and published papers is that CIS will progress to invasive cancer in only a very small proportion of cases if at all. This inference is incorrect and reliance on it has been dangerous for patients.

The criticisms of the McIndoe et al paper do not stand up to examination. There are a few minor uncertainties in interpretation but these do not detract seriously from the general findings. A more reliable inference as to the invasive potential of CIS can be drawn from that paper than from Dr Green's publications.

1. Journal of Obstetrics & Gynaecology of the British Commonwealth Vol 73, 897. Dec. 1966
2. 1969 Int. J. Gynaecology & Obstetrics, 157.
3. Aust.NZ J.Obstet.Gynaec. (1970) 10: 41.
4. Journal of Obstetrics & Gynaecology of the British Commonwealth Vol 77, No.1, Jan 1970, 1.
5. 'The Progression of Pre-invasive Lesions of the Cervix to Invasion'. The NZ Medical Journal No. 525, Oct 9, 1974, 283.
6. McIndoe et al, Journal of the American College of Obstetricians and Gynecologists, 'Obstetrics & Gynecology' Vol 64, No.4, Oct. 1984, 451.
7. 'Cervical Carcinoma in Situ' Aust.NZ J.Obstet.Gynaec (1970) 10; 41, 47.
8. 'An "Unfortunate Experiment" At National Women's'. Metro, June 1987
9. International Surgery. Vol 47 No 6 512
10. 'Cervical Carcinoma in Situ: True Cancer or Non-Invasive Lesion?' Aust.NZJ.Obstet.Gynaec (1964) 4; 165, 167.
11. Cervical Cancer in New Zealand – A Failure of Cytology?' Asia-Oceania J.Obstet.Gynaecol. December 1981, Vol 7, No.4; 303-313, 303.
12. 'Cervical Cancer and Cytology Screening in New Zealand' British Journal of Obstetrics & Gynaecology 1979; 86: 671-2.
13. 'Human Experimentation: a guided step into the unknown' W.A. Silverman, O.U.D. 1985