

APPENDIX 3

MEDICAL REVIEW

Introduction

A review was undertaken by the medical advisers to the Commission, Professor Eric MacKay, Professor of Obstetrics and Gynaecology, University of Queensland, Dr Charlotte Paul, Epidemiologist, University of Otago Medical School and Dr Linda Holloway, Pathologist of the University of Otago Wellington School of Medicine. The principal purpose of the review was to determine whether any patients required further treatment or advice or both as specified under Term of Reference 3.

The secondary reason for the review was to determine whether the conclusions of the paper by McIndoe et al 'The Invasive Potential of Carcinoma in Situ of the Cervix'¹ were soundly based. A criticism of that paper had been that the total number of cases included in the study were fewer than the total number of patients registered at the Hospital with CIS of the cervix over the period specified.

This review also enabled us to provide further analyses of these data which may shed some light on the occurrence of "missed invasions", and on the subsequent diagnosis of invasion, during the time period that the "1966 policy" was in practice.

CARCINOMA IN SITU OF THE CERVIX 1955-1976

Methods

The sources of information used to identify patients for this review were:

1. The lists of Group 1 and Group 2 patients made available by the McIndoe Estate. These lists include patients with microinvasive carcinoma (called CIS with microinvasion in this review).
2. The histology work cards used by Dr MR McLean at NWH: copies of these cards were made available to the Commission by the Hospital Board.
3. The coding forms prepared for data entry on the Postgraduate School Computer: copies of these were not made available, but access was arranged for the medical advisers to view these at NWH.
4. File cards from the McIndoe Estate.
5. Reports appended to the brief of evidence of Dr R Jones.

The list of patients with a diagnosis of CIS of the cervix from the NWH Cancer Register was used as the master list. However, where names appeared on the McIndoe lists which were not included in the Cancer Register lists, these cases were added to the final lists.

NOTE: Microinvasive carcinoma has been classified as Stage O cervical cancer at NWH, thus it is included in this review. The working principle has been to include as cases of CIS, those patients who were treated as CIS at the outset.

All patients were allocated to a category depending on their inclusion in the McIndoe paper, their reason for exclusion from that paper, and a miscellaneous category of exclusions. The notes of patients missing from either the Cancer Register or the McIndoe lists were examined to determine the reason for their exclusion.

All patients who had a subsequent diagnosis of invasion (not including microinvasion) were noted. Information about this diagnosis was taken from the McIndoe paper, including extra tables where the cases were identified; from the information prepared by Dr R Jones on cases of CIS with microinvasion and on cases with continuing positive cytology; and from Dr McIndoe's card file.

The review presented by Dr Jamieson and Dr Mackintosh was scrutinized for any further cases. The diagnoses of Dr McLean which formed the basis of pathological diagnosis for cases included in the 1984 paper were accepted. There were a few cases which seemed to have had a histological diagnosis of invasion which was disregarded clinically and have not subsequently been treated as invasion. These cases have not been included as having a subsequent diagnosis of invasive cancer.

A review was undertaken of the CC case notes of the following categories of patients to determine if they required further clinical review:

1. Patients with positive follow-up cytology at two years (Group 2 of the McIndoe paper).
2. All patients with punch or wedge biopsy only not included in (1) above (from Group 1 of the McIndoe paper).
3. All other Group 1 patients with a histological report of incomplete excision at the final operative procedure.
4. Patients excluded from the McIndoe paper because of evidence of continuing disease and no final histological diagnosis.
5. Patients excluded from the McIndoe paper because they had been followed for less than 5 years after diagnosis.
6. Patients excluded from the McIndoe paper because they had a diagnosis of CIS with microinvasion.
7. All other excluded patients. In addition the case notes of a few patients who gave evidence to the Commission who were diagnosed outside the time period 1956-1976 have been reviewed.

The criteria used to determine whether patients required further clinical review and follow-up were based on Dr Jordan's recommendations:

1. Patients with persistent or recurrent abnormal cytology following treatment.
"Any patient with persistent abnormal cytology following treatment should be reviewed by colposcopy and cytology and this to include an endocervical cytology specimen and endocervical curettage, with a view to intervention if persistent abnormality is suspected.These cases should be reviewed as a matter of urgency by a colposcopist.
2. Patients who have had in the past a diagnosis of microinvasive carcinoma, and where there is some doubt about adequacy of treatment.
"All case records should be reviewed by the Hospital authorities, to assess first, if treatment has been adequate and is the patient thought to be free of disease, and second, is further intervention required."
3. Patients whose last operative procedure showed incomplete excision and where there is some doubt about the possibility of ongoing disease.
"If there is any suspicion that the immediate follow-up period did not include colposcopy and adequate cytology, then the patient should be recalled."
4. Patients whose only treatment was punch or wedge biopsy.
"The case records of all these patients should be reviewed and if there is any suspicion that there may be ongoing abnormality, then the patient should be reviewed by a colposcopist."

5. Patients who have developed invasion.
6. Patients who have probably been adequately treated.
"All these patients require lifelong follow-up by cytology."

Results

There were 1194 cases on the cancer register. A further 34 cases were added from the McIndoe lists. Ten of these cases were from the 12 cases of CIS in whom a diagnosis of invasion was made within 12 months. Of the total 1228 cases, 1028 were included in the McIndoe paper. There were 200 cases which appear not to have been accounted for in the paper.

The majority of these were patients who had a diagnosis of "carcinoma in situ with microinvasion" either at the outset or during the course of follow-up. In addition there were at least 37 patients who were seen for consultation only at NWH and had their definitive treatment elsewhere. We found three cases where a diagnosis of invasive cancer appeared to have been made at the outset.

It was appropriate that these cases should have been excluded from the paper by McIndoe et al as the patients did not have an earlier diagnosis of CIS. However, their inclusion in the site register as cases of CIS suggests that these cases were regarded by some clinicians as having less than invasive cancer.

We have noted a number of cases of this sort, where there has been debate about the initial histology. We accept that Dr McLean's review of the original histology will have led to the final classification. Nevertheless, an independent review of the histological diagnosis of these cases should be undertaken if there is to be a final scientific assessment of progression to invasion and the outcome of treatment at National Women's Hospital. It is not expected that such a review of this aspect would change the findings of the publication of McIndoe et al in a significant manner. However, if a substantial proportion of microinvasive cases on review were reclassified as CIS only and included in the analysis, then the progression rates would be higher than calculated in the original publication.

There were 33 patients where the reason for exclusion from the McIndoe paper was not known. Some of these patients also will have had their definitive treatment elsewhere. For others, they may have been regarded as less, or more, than CIS on histological review. It is important that the case notes reveal that for almost all the unaccounted exclusions, treatment had been orthodox. None of these cases was subsequently diagnosed as invasive cancer and treated as such, though in three cases there was, again, debate about the histology. Thus the inclusion of this group into the McIndoe paper would be unlikely to have altered the conclusions of the paper.

One case included in the McIndoe paper was excluded from this analysis as her initial treatment for CIS was not at NWH, although the histology was reported from NWH. A further two cases were transferred to the year of first diagnosis of CIS. Two further cases appeared to have had their first diagnosis at other hospitals, but were referred to NWH with positive smears and a further diagnosis of CIS established.

Table 1 shows the number of women who had a first diagnosis of CIS of the cervix, by year of first diagnosis, and subsequent diagnosis of invasive cancer. As this proportion depends on the time period over which they were followed, this has been calculated over 10 years from diagnosis of CIS, for each calendar year. The results are shown in Table 2. For the years 1955-59 2/126 (1.6%) proceeded to invasion over the subsequent 10 years. For the time period 1960-64, the proportion was almost the same at 5/321 (1.6%). For the next time period, 1965-69, the proportion rose to 18/208 (8.7%). In 1970-74 the proportion continued to be high at 20/286 (7.0%), but it fell sharply in the last time period, 1975-76, to 5/287 (1.7%).

The preceding analysis includes cases where the subsequent diagnosis of invasion was made within one year of the diagnosis of CIS. If these cases are excluded from the analysis, on the basis that they might represent missed invasions, and the proportion proceeding to invasion over one to 10 years is calculated, the same pattern can be seen (Table 2). This is shown graphically in Table 4.

The occurrence of cases proceeding to invasion over less than one year is investigated further in Table 3. The number and proportion of cases rose in the 1965-1974 time period. This higher rate of "missed invasions" over the time period of the management proposed in 1966 suggests that an increase in "missed invasions" was a consequence of this policy, and that the policy had altered by the final time period.

The table also shows that at least seven missed invasions had occurred prior to 1970, when the paper by Green and Donovan was published.

The review of files undertaken by the Commission's medical advisers resulted in advice to Judge Cartwright that certain patients in the following categories required further treatment or advice, if this had not already been done:

1. Patients with persistent or recurrent abnormal cytology following treatment (20 patients). In this category is a group of patients who were lost to follow-up still with persistent abnormal cytology.
2. Patients who had a diagnosis of microinvasive carcinoma and where there was some doubt about adequacy of treatment (13 patients).
3. Patients whose last operative procedure showed incomplete excision and there was some doubt about the possibility of ongoing disease (13 patients).
4. Patients whose only treatment was punch or wedge biopsy (5 patients).
5. Other special need for follow-up (17 patients).

Conclusions

A selective review of the case notes of patients diagnosed as CIS of the cervix and managed at NWH from 1955 to 1976 has been undertaken. The names of 68 patients in this category were referred to Judge Cartwright (summary above). Most cases excluded from the McIndoe paper have been accounted for and the reason for exclusion documented. Of the small number which are unexplained, it is very unlikely that their inclusion would have altered the conclusions of that paper.

The outcome of the management of CIS at NWH, in terms of preventing the development of invasive cancer over the subsequent 10 years, has been reviewed. It is clear that there was a marked and statistically significant elevation in risk of developing invasion within one to 10 years for patients treated during the years 1965 to 1974, compared with the time periods before and after.

These rates do not take into account the age of patients. When we examined the age distribution of the cases included in the McIndoe paper by year of diagnosis of CIS, we found the age distributions similar for the time periods 1955-1964 and 1965-1974. Therefore differences in age could not explain the observed increase in risk of invasion in the 1965-1974 time period. However, the women diagnosed with CIS in 1975-1976 were on average younger than those diagnosed earlier. Thus the decline in risk of invasion in the most recent time period must be interpreted with caution. The exclusion of patients lost to follow-up and those patients whose definitive initial treatment was not at NWH did not materially affect the results.

The proportion of patients who had a diagnosis of invasive cancer within one year of the original diagnosis of CIS also rose during the same time period. This suggests that management during those years did not result in adequate exclusion of invasive cancer at the outset.

It is possible that there are additional patients where the cancer was truly invasive at the outset. This is suggested by two other cases where there is in the notes a histological diagnosis of invasion which was not treated clinically as such. We have accepted that these diagnoses were reviewed by Dr McLean for the 1984 McIndoe publication, and were regarded as CIS initially, but clearly there may be room for debate. Thus even more patients than the 12 noted may represent "missed invasion".

The management of CIS subsequent to 1976 has been reviewed by Drs Jamieson and Mackintosh and for three years only by Dr Jones. Their results are in general agreement, that the proportion of CIS cases diagnosed from 1977 to 1979 proceeding to invasion is again less than 2%.

The analysis of outcome in patients with CIS shown here differs from the analysis in the McIndoe paper. In that paper, patients were divided into groups according to the presence or absence of evidence of continuing disease, in order that progression rates could be estimated. The outcome of different methods of treatment was not examined directly (although there were marked differences in treatment between the two groups, particularly in completeness of excision).

In contrast, in this analysis the aim has been to examine outcome according to the time period of initial diagnosis and treatment, so that any effect of changes in treatment methods over time could be observed.

Clearly, as in the overall analysis by McIndoe and colleagues, many of the patients in any year were treated by generally accepted methods, so that the proportion subsequently diagnosed as invasion must represent much less than the true progression rate.

CARCINOMA IN SITU OF THE CERVIX

1977-1986

A limited review of these cases was undertaken. The list of patients with a diagnosis of CIS for those years compiled by Dr Jamieson and Dr Mackintosh was used as a master list. All cases were noted where:

1. There was a diagnosis of microinvasion and treatment was less than hysterectomy.
2. There was incomplete excision recorded.
3. Management had been by punch or wedge biopsy only.
4. There was no follow-up recorded.

The case notes of patients falling into these categories were reviewed. After review a total of 51 names were referred to Judge Cartwright, 32 of these were cases with a diagnosis of microinvasive cancer.

CARCINOMA IN SITU OF THE VAGINA

(a) 1955-1976

We have identified 19 cases with CIS of the vagina over this time period. All but four of these patients had had an earlier diagnosis of CIS of the cervix at National Women's Hospital, and thus had already been reviewed as part of the review of CIS of the cervix cases. Of the other four patients, three had had a prior hysterectomy, two following abnormal smears. One patient was referred to National Women's Hospital following treatment for invasive cancer of the vagina. The recurrent lesion was regarded as CIS of the vagina at National Women's Hospital.

Overall, at least 15 and possibly 17 of these 19 patients had a history of cervical neoplasia. Recurrence or persistence of the cervical disease in the vaginal vault must be the

most likely possibility in this group. Review of the case notes showed that four patients currently had evidence of continuing disease, with cytology reported as class 2R-5. Three of the patients had already been referred to Judge Cartwright for follow-up. The fourth patient's name has also now been referred.

The outcome in this group of patients showed that 13 out of the 19 subsequently developed invasive cancer, and seven were known to have died of malignant disease. Two patients died of other causes, one with continuing CIS, and the other some time after radiation treatment of her CIS.

(b) 1977-1986

Only two cases appear to have been diagnosed during this time period. One of these cases was referred to Judge Cartwright for clinical review.

It is unlikely that all cases of CIS of the vagina have been identified. However staff at NWH have probably identified all those cases who had a vaginal lesion only. Any other cases with a prior cervical lesion, would have been reviewed with the cervical cases.

No detailed assessment was made of the progression rate in these cases. However, from the information provided here it can be seen that 68% of the patients originally diagnosed between 1955 and 1976 subsequently developed invasive cancer, and 37% have died of their disease. A detailed scientific assessment should be made of the outcome among these patients.

CARCINOMA IN SITU OF THE VULVA

A review was undertaken of all cases diagnosed after 1983. All earlier cases had been reviewed in the publication by Jones and McLean.² The review of later cases was carried out to determine whether any cases required further advice or treatment. Seventeen cases were reviewed. Two cases were referred to Judge Cartwright.

SUMMARY

The review of case notes of patients with a diagnosis of carcinoma in situ of the genital tract who were managed at NWH was undertaken primarily to determine whether any patients required further treatment, or advice or both as specified under Term of Reference 3.

The criteria used to determine whether patients required further clinical review and follow-up were based on Dr Jordan's recommendations. The lack of knowledge which patients interviewed by Judge Cartwright displayed about their disease and about the need for follow-up cytology influenced decisions to recommend further advice.

The names of 123 patients were referred to Judge Cartwright in order that suitable follow-up could be arranged.

1. *Obstetrics and Gynecology* 64 : 451, (1984)
2. 'Carcinoma In Situ of the Vulva: A Review of 31 Treated and Five Untreated Cases' *Obstetrics and Gynecology* (1986) 68 : 499

TABLE 1

SUBSEQUENT DIAGNOSIS OF INVASION IN 1228 PATIENTS
WITH AN ORIGINAL DIAGNOSIS OF CIS
FROM 1955 TO 1976

Year of First Diagnosis	No. of Cases	Subsequent Diagnosis of Invasion	% Subsequently Diagnosed as Invasion
1955	6	—	—
1956	15	—	—
1957	40	—	—
1958	32	3	9.4
1959	33	2	5.1
1960	60	3	5.0
1961	45	2	4.4
1962	47	2	4.3
1963	83	4	4.8
1964	86	4	4.7
1965	60	2	3.3
1966	39	5	12.8
1967	38	5	13.2
1968	30	5	16.7
1969	41	5	12.2
1970	61	7	11.4
1971	47	3	6.4
1972	54	6	11.1
1973	55	4	7.3
1974	69	7	10.1
1975	115	4	3.5
1976	172	1	0.58
TOTAL	1228	74	6.0

TABLE 2

SUBSEQUENT DIAGNOSIS OF INVASION WITHIN 10 YEARS
OR LESS OF ORIGINAL DIAGNOSIS OF CIS
IN 1228 PATIENTS FROM 1955 TO 1976

(Percentages in parenthesis)

Year of First Diagnosis	No. of Cases	Diagnosis of Invasion In < = 10 Years	Diagnosis of Invasion In 1-10 Years
1955	6	—	— (0.0)
1956	15	—	— (0.0)
1957	40	—	— (0.0)
1958	32	1 (3.1)	1 (3.1)
1959	33	1 (3.0)	— (0.0)
1960	60	1 (1.7)	1 (1.7)
1961	45	—	— (0.0)
1962	47	1 (2.1)	1 (2.1)
1963	83	2 (2.4)	1 (1.2)
1964	86	1 (1.2)	1 (1.2)
1965	60	1 (1.7)	1 (1.7)
1966	39	5 (12.8)	2 (5.1)
1967	38	4 (10.5)	3 (7.9)
1968	30	5 (16.7)	4 (13.3)
1969	41	3 (7.3)	3 (7.3)
1970	61	4 (6.6)	4 (6.6)
1971	47	3 (6.4)	3 (6.4)
1972	54	4 (7.4)	2 (3.7)
1973	55	4 (7.3)	3 (5.5)
1974	69	5 (7.2)	4 (5.8)
1975	115	4 (3.4)	3 (2.6)
1976	172	1 (0.58)	1 (0.58)
TOTAL	1228	50 (4.1)	38 (3.1)

CERVICAL CANCER REPORT

TABLE 3

CASES WHERE THE ORIGINAL DIAGNOSIS WAS CIS CERVIX
AND WHERE INVASION WAS SUBSEQUENTLY DIAGNOSED
WITHIN ONE YEAR

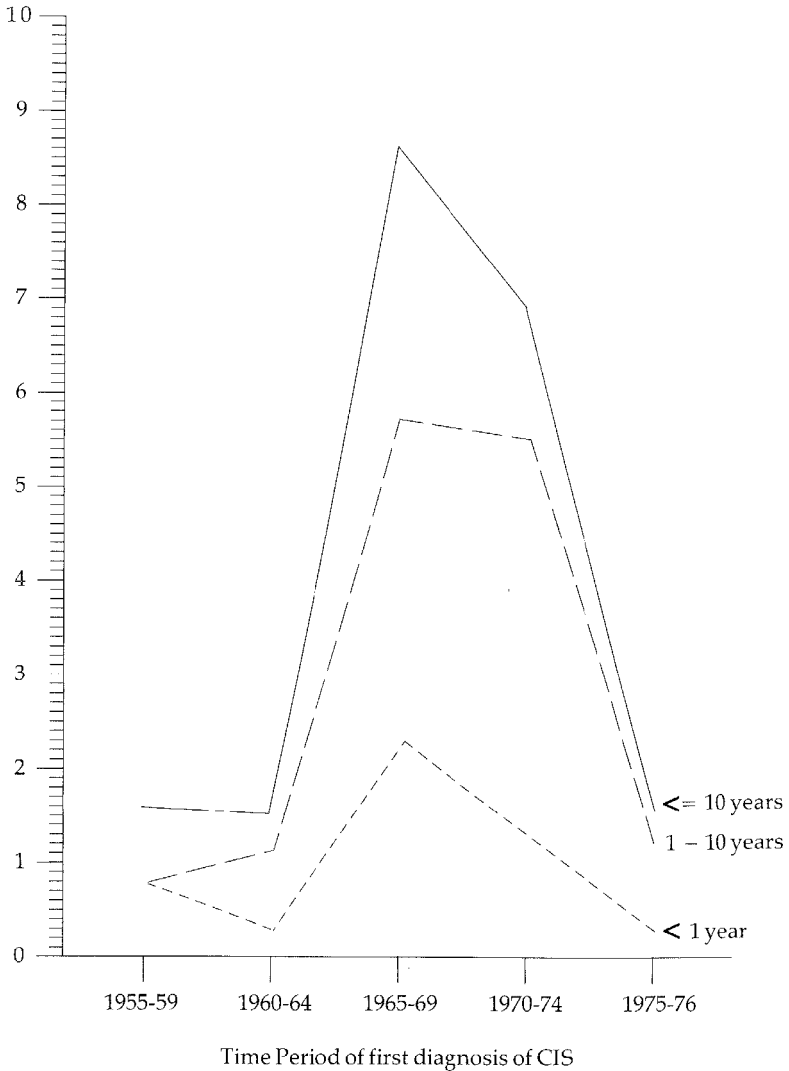
(Includes cases where the original
diagnosis was CIS with microinvasion)

Year Of First Diagnosis	No. Of Cases	% Of All Cases Of CIS By 5-yr Time Period
1955	-)	
1956	-)	
1957	-)	1/126 (0.79%)
1958	-)	
1959	1)	
1960	-)	
1961	-)	
1962	-)	1/321 (0.31%)
1963	1)	
1964	-)	
1965	-)	
1966	3)	
1967	1)	5/208 (2.4%)
1968	1)	
1969	-)	
1970	-)	
1971	-)	
1972	2)	4/286 (1.4%)
1973	1)	
1974	1)	
1975	1)	
1976	-)	1/287 (0.35%)
TOTAL	12	12/1228 (0.98%)

TABLE 4

SUBSEQUENT DIAGNOSIS OF INVASIVE CANCER WITHIN
TEN YEARS OF ORIGINAL DIAGNOSIS OF CIS
IN 1228 PATIENTS FROM 1955 TO 1976

Percentage subsequently
diagnosed with invasion



APPENDIX 4

LIST OF ASSOCIATE PROFESSOR GREEN'S RELEVANT PAPERS

1. **Carcinoma in Situ of the Uterine Cervix**
The Australian & New Zealand Journal of Obstetrics and Gynaecology (1962) 2:49
2. **Cervical Carcinoma in Situ: True Cancer or Non-Invasive Lesion?**
The Australian & New Zealand Journal of Obstetrics and Gynaecology (1964) 4:165
3. **Cervical Cytology and Carcinoma in Situ**
The Journal of Obstetrics and Gynaecology of the British Commonwealth (1965) 13
4. **The Significance of Cervical Carcinoma in Situ**
American Journal of Obstetrics and Gynecology (1966), Vol 94, No.7, 1009
5. **Cervical Cone Biopsy with Octapressin**
Australian & New Zealand Journal of Obstetrics and Gynaecology (1966) 6: 259
6. **Pregnancy following Cervical Carcinoma in Situ**
Journal of Obstetrics and Gynaecology of the British Commonwealth (1966) Vol 73, 897-902
7. **Is Cervical Carcinoma in Situ A Significant Lesion?**
International Surgery (1967), Vol 47, No. 6, 511
8. **Invasive Potentiality of Cervical Carcinoma in Situ**
International Journal of Gynaecology and Obstetrics (1969) Vol 7, No. 4, 157
9. **Vaginal Carcinoma in Situ Following Hysterectomy**
(McIndoe and Green) (1969) Acta Cytologica Vol 13, No.3, 158
10. **Cervical Carcinoma in Situ**
Australian & New Zealand Journal of Obstetrics and Gynaecology (1970) 10:41
11. **The Natural History of Cervical Carcinoma in Situ**
(Green and Donovan) The Journal of Obstetrics and Gynaecology of the British Commonwealth (1970) Vol 77, No.1, 1
12. **Duration of Symptoms and Survival Rates for Invasive Cervical Cancer**
Australian & New Zealand Journal of Obstetrics and Gynaecology (1970) 10: 238
13. **The Progression of Pre-invasive Lesions of the Cervix to Invasion**
The New Zealand Medical Journal (1974) Vol 80, No. 525, 279
14. **Cervical Cancer : Detection and Treatment**
Patient Management, (1977), 83
15. **Cervical Cancer and Cytology Screening in New Zealand**
British Journal of Obstetrics and Gynaecology (1978) Vol 85, No.12, 881
16. **Cervical Cancer in New Zealand – A Failure of Cytology?**
Asia-Oceania Journal of Obstetrics and Gynaecology (1981) Vol 7, No. 4, 303.