

APPENDIX 9

DECLARATION OF HELSINKI

10th World Medical Assembly 1964
Revised 35th World Medical Assembly, Venice 1983

HUMAN EXPERIMENTATION

In 1964, the World Medical Association drew up a code of ethics on human experimentation. This code, known as the Declaration of Helsinki, as amended by the 29th World Medical Assembly, Helsinki, Finland, in 1975, and by the 35th World Medical Assembly, Venice, Italy, in 1983, reads:

It is the mission of the medical doctor to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration"; and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research, a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, The World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects.

They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human

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- subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with the medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
 4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objectives is in proportion to the inherent risk to the subject.
 5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
 6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
 7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
 8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
 9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
 10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
 11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
 12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

**II. Medical Research combined with Professional Care
(clinical research)**

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proved diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1,2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

**III. Non-therapeutic biomedical research involving
human subjects
(Non-clinical biomedical research)**

1. In the purely scientific application for medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

APPENDIX 10

CONSULTATION CLINIC NOTES, NATIONAL WOMEN'S HOSPITAL

PATIENT CODE 10G

-11.73 This patient was admitted through the Colposcopy Clinic for inpatient biopsy following a series of positive cytology.

-11.73 **E.U.A. COLPOSCOPY, RING BIOPSY OF CERVIX, D & C**
Prof. G

Indication: Class 4 cervical smear – no abnormal symptoms.

Colposcopic Findings Anterior lip shows marked transformation zone with irregular tongues of metaplastic epithelium but no raised areas or abnormal capillary patterns. Posterior lip shows several leukoplakic areas on the basis of metaplastic epithelium. Neither macroscopically or colposcopically can this be described as suspicious. The cervix is somewhat hypertrophied in both anterior and posterior lips and deficient laterally but not unusually so. Uterus normal size, shape and position and no adnexal abnormalities.

Procedure: Ring biopsy taken from all round the external os excising the greater part of the transformation zone on the anterior lip and all the altered area showing leukoplakic changes on the posterior lip. The ring was removed in two portions as though the ring had been opened at 3 o'clock and 9 o'clock. The cervix was dilated to 8 Hegar and normal looking cervical and endometrial curettings obtained. Cervix repaired with 2 inverting sutures. Prof.G

PATH REPORT: Ring biopsy at 3 & 6 o'clock
Carcinoma in situ of cervix.

Posterior lip of cervix.
Carcinoma in situ of cervix.

Endocervical curettings:
Sections fragments of myometrium, isthmus endometrium and
Endocervical tissue.

Endometrial curettings:
Hormone attenuated endometrium.

Condition satisfactory.

28.11.73 Discharged. To return to clinic in two months.

AC 31.1.74

7.3.74	Patient is well, has a little bit of spotting still, normal periods. Cervix is well healed, uterus a little bit bulky, anteverted and mobile and she is to continue with steriodal contraception. See in 6 months query switch to another oral contraceptive to control the bleeding but I think that it will probably have settled down by then. Smear taken. Dr H SMEAR: A2 repeat next visit.	7.3.74 53.5 AC 12.9.74
8.8.74	See copy of letter to Dr... The patient stated that she has been well apart from vaginal spotting on and off since the operation. Neogynon and Norinyl-2 have been taken but spotting continued. Physical and vaginal examination revealed normal findings with a well [words missing] any side effects. See in 6 months. Dr K. SMEAR: Grade 2 repeat next visit.	58.5kg AC30.1.75
6.3.75	Patient is well, is now taking Serial C and has normal regular periods with no intermenstrual or post coital bleeding. On examination cervix healthy, smear taken. Bi-manual examination uterus normal size, anteverted, mobile. See in 6 months. Dr H M SMEAR: Grade 4	54.5 AC 4.9.75
2.10.75	This patient is perfectly well and continues to take Serial C. Her periods are regular and no intermenstrual or post coital bleeding. On examination cervix looks perfectly healthy but on bimanual examination feels rather hard. This may well be secondary to her ring biopsy but in view of her grade 4 smear the situation was discussed with Prof. G who felt that we should see her again in 6 months' time. Smear taken. Dr D SMEAR: Grade 4	54.0 AC 8.4.76 29.4.76
29.4.76	She had a ring biopsy on the 27.11.73 showing carcinoma in situ of the cervix. On 6.3.75 and 2.10.75 she had 2 grade 4 smears. Her periods are regular – no intermenstrual or post coital bleeding. She has been very well. On pelvic examination – very small polyps and red area on the posterior lip – also seen by Professor G. On bi-manual palpation the uterus is normal in size, no adnexal mass. Professor G considers that she should be in the hospital for a repeat ring biopsy in the near future. Smear has been taken. Dr S SMEAR: Grade 4.	57.5 kgs Admss.
17.5.76	Re-admitted.	
18.5.76	COLPOSCOPY. RING BIOPSY OF CERVIX, D & C Dr.S Indication: Grade 4 smear with carcinoma in situ, 27.11.73. Ring biopsy. Findings: At follow-up clinic she had grade 4 smears on 6.3.75, 2.10.75. Last seen 29.4.76. Colposcopy: Both anterior and posterior lips just near the canal had wide areas of coarse punctation but no obvious area of	

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abnormality. She is menstruating at the moment. On macroscopic examination the cervix had an irregular surface following previous conization. Hypertrophy on both anterior and posterior lips and rather ? but no obvious lesions. Uterus small in size and shape. No adnexal mass.

Procedure: Ring biopsy taken from all around external os deep into the canal. Because of the shortening of the cervix it was very difficult to go too deep. Ring opened at 3 o'clock. Cervix dilated to Hegar 8. Few curettings were obtained. Dr S

PATH REPORT: **Cone biopsy of cervix opened at 3 o'clock**
 Sections show carcinoma in situ mainly on the anterior lip. The excision is incomplete. Carcinoma in situ cervix.

Curettings:
 Sections show hormone attenuated endometrium. In addition there are two small fragments of squamous epithelium showing severe dysplasia.
Hormone attenuated endometrium.

Condition satisfactory.

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| 19.5.76 | Discharged. To return to clinic in one month. | AC 17.6.76 |
| 17.6.76 | This patient had ring biopsy 18.5.76 – carcinoma in situ. Excision incomplete. Apart from being frightened to be examined, she does not have any complaints. On examination the cervix well healed, no other abnormality seen. Smear taken. See in 6 months. Dr S | 56.5 kgs
AC 16.12.76 |
| 16.12.76 | Patient stopped Nordiol 6 weeks ago and she had some spotting a few times afterwards, otherwise she has been well. [Her partner] is using condoms now. On examination the cervix looked normal, vagina and vulva looked normal. Uterus is not enlarged, no adnexal mass. See 6 months. Smear taken. Dr S | 57.5 kgs
AC 23.6.77 |
| 23.6.77 | Mrs – is well and continues to gain weight. She is having regular menstrual periods with no intermenstrual bleeding. The last smear was grade 2R. On examination the cervix looks irregular but otherwise normal. Bimanually no abnormality was detected. Smear taken. See 1 yr. Dr J | 61.5
AC 22.6.78
24.8.28
14.9.78 |
| -9.78 | In excellent health, no symptoms referable to the genito-urinary system. On physical examination the abdomen is normal, no inguinal nodes, the vagina/vulva/cervix all | 63.5kg |

	appear normal. Bimanual examination the adnexae are normal and there are no masses. Uterus is small and anteverted in position. Smear taken. See 1 year.	
	SMEAR: Grade 4.	Dr.M AC 13.9.79 29.3.79
	Atypical cells consistent with carcinoma-insitu.	
29.3.79	Terrified that she is going to die of cancer. Looks extremely well, periods she says are now becoming smaller and that she occasionally skips a month. The cervix looks normal with a fairly wide os and apart from the puckering of the squamous epithelium on the posterior lip of the cervix one would not think she had ever had a cone biopsy done. There was no bleeding on probing in the endocervical canal. Smear taken. Arrange for further biopsy. She is very panicky but not too difficult to reassure.	62.0kg Prof G
	SMEAR: Grade 4. Atypical cells consistent with insitu or invasive lesion.	Admiss
14.5.79	Re-admitted.	
15.5.79	E.U.A. CONE BIOPSY OF CERVIX. D & C Prof G	
	Indications: Repeated positive smears following cone biopsy diagnosis of carcinoma-insitu first formed in Nov 73. Patient has never had any symptoms.	
	Findings: Normal vagina but very lax introitus and with some moderate degree of utero vaginal prolapse. The cervix apart from the sharp squamo columnar junction looks as though it had never had a biopsy before and the external os was fairly widely dilated. Small transformation zone all around the external os within an area of punctate epithelium about ½ x ½ cm visible colposcopically on the left lip. Depth of uterine cavity 8½ cm. No uterine or adnexal abnormalities.	
	Procedure: Ring biopsy taken from all around the external os to a depth of about 5-7mm then excising the area of atypicality referred to. Cervix repaired with lateral sutures, fairly profuse endometrial curettings obtained. Slight bleeding.	Prof G
	Path Report: Cone biopsy of cervix opened at 6 o'clock Sections show carcinoma-insitu with foci of microinvasion in blocks F & J. Excision is incomplete at the endocervix in blocks M & N and on the deep surface in H & J. Adenocarcinoma-insitu is seen in block K. A minor degree of "Pill" cervix is seen. Carcinoma-insitu with microinvasion. Adenocarcinoma-insitu. "Pill" Cervix.	
	Curettings: LMP 20.4.79 Sections show Hyperplastic endometrium.	

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16.5.79	Discharged to return to clinic.		AC 19.7.79
-/8/79	Had a cone biopsy in May for a grade 4 smear. The histology showed carcinoma in situ with microinvasion and Adenocarcinoma in situ. Has been well. L.M.P. 2.8.79. No intermenstrual or post coital bleeding. On examination the cervix appeared reduced in size, had healed completely and there was no abnormality seen. Smear taken. Uterus anteverted, normal size and no adnexal masses. The histology report will be treated just as a carcinoma in situ. Discussed with Prof. G Review in 6 months.		9.8.79 62 Kg AC 21.2.80
-3.80	SMEAR: Grade 1	Dr N	6/3/80
5.3.81	Patient has been quite well for the last 6 months. Her periods are becoming irregular as she approaches the menopause but she has had no intermenstrual bleeding and no abnormal vaginal discharge. Abdominal examination normal. Vagina appeared healthy as did the cervix with just a pinhole external os visible. Smear taken. Bimanual examination n.a.d. See in 1 year.		61 kg
5.3.81	Looks and feels well. She has had no trouble or problems since last visit. Her periods are irregular and have been over the past 2 years, but has no dysmenorrhoea or hypermenorrhoea. She feels sometimes hot flushes but these do not bother her. No abnormal bleeding or discharge. On general examination no abnormalities can be seen. On pelvic examination uterus anteverted, slightly enlarged but non-tender, both parametria normal. Cervix is covered with squamous epithelium with just a pinhole external os. Smear taken from the ectocervix. See in 1 year.	Dr T	AC 4.3.82
1.10.81	SMEAR: Grade 3 Cells present are suggestive of severe dysplastic to carcinoma-in-situ lesion.		62.5 kg
1.10.81	Last smear was class 3 but there was some doubt about the diagnosis from Dr K. The cervix looks 100% normal except for the rather stenosed external os which is only 1-2mms in diameter. She has not had a period for 3 months and might be about to get one and I hope that this is not because of the cervical stenosis. The uterus feels normal size and is not tender. Smear taken. See in 6 months.		AC 1.4.82
-6.82	SMEAR: Grade 3 Cells present are suggestive of severe dysplasia to carcinoma-in-situ lesion.	Prof.G	60.5
-6.82	Patient was seen today at the clinic by Dr J. Breast examination was normal. She feels well except for some hot flushes at night. She has not had a period for 6 months. She has had no other vaginal bleeding or discharge. On examination the uterus was anteverted, non-tender, the cervix was small and stenosed. Smear taken. See in 6 months.		AC 2.12.82
	SMEAR: Grade 1	Dr J	16.12.82 11.8.85

22.9.83	Patient seen today at Clinic. She has a long history of abnormal cervical smears and ring biopsies have shown this to be carcinoma in situ. In the last 12-18 months, she has remained symptom free and has had two smears, both Grade 1. At present she is well, has no post coital bleeding, intermenstrual bleeding or discharge and the last period was in February. She has some post menopausal symptoms and it would seem that she is going through the change. O/E she has a tender lymph node in the left inguinal area but this [last line indistinguishable].	22.9.83 66kg
22.9.83	continued...vaginal examination. The cervix was stenosed. Epithelium was intact. A smear has been taken. Uterus non tender, anteverted, mobile. I have informed her that she must not now regard vaginal bleeding as "menopausal" and any bleeding that occurs at this stage should probably be investigated. We will see her in six months.	Dr P 15.3.84
	SMEAR: Grade I	26.4.84 67.5 155/85
26.4.84	Quite well, no problems. Smear taken. VE normal. See one year.	Dr J
	SMEAR: Grade 1	AC 2.5.85
3.5.85	Quite well. No symptoms. See in 1 year.	65.5kg 130/85
	SMEAR: Dysplastic abnormalities present; (Grade 2R) The cellular changes indicate mild dysplasia.	AC 1.5.86 26.6.86 66kg 140/150
26.6.86	Mrs – is well and has no complaints apart from some fear from coming here. She cannot remember when she last had a period but it is some years ago at least. No abnormality found on examination of breasts and abdomen. Pelvic examination shows vulva, vagina and cervix to be healthy in appearance. Uterus not defined but certainly not grossly abnormal. I have warned her that if there is any abnormality shown in this smear, we will ask her to come back for a colposcopy or biopsy. Otherwise review in one year. Mr W	
	SMEAR: DYSPLASTIC ABNORMALITIES PRESENT. Grade 2R Occasional dysplastic cells are identified.	AC 25.6.87
78.86	See copy of referral to Colposcopy Clinic from Mr W.	AC 14.8.86
16.20.86 [16.12.86]	The colposcopic examination done by...showed a small area of possible dysplasia around the os but no abnormality was seen on the rest of the ectocervix or on the upper vagina. The cervical canal could not be viewed. Taking all characters into account I think it is reasonable to do a hysterectomy rather than to precede this with another cone biopsy. Mrs – is quite happy to have a hysterectomy although she worries about the anaesthetic and she is very unhappy about vaginal examination.	

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She is going to Australia next month and I have said that we will do our best or admit her for operation in February 1987.

Mr W

[This patient was readmitted for a hysterectomy in September 1987]

LABORATORY SERVICES REPORT (Received Laboratory 1.10.87)

Previous Histology:

- NW73/7674 Endocervical Curettings. Endocervical tissue.
- NW73/7675 Endometrial Curettings. Hormone attenuated endometrium.
- NW73/7672 Ring biopsy at 3 and 6 o'clock
- NW73/7673 Posterior Lip. Carcinoma in situ of the cervix.
- NW76/3377 Cone biopsy of cervix opened at 3 o'clock. Carcinoma in situ of the cervix.
- 3378 Curettings. Hormone attenuated endometrium.
- 79/3067 Cone biopsy of cervix opened at 6 o'clock. Carcinoma in situ with microinvasion. Adenocarcinoma-in-situ. "Pill" cervix.
- 79/3068 Curettings. Hyperplastic andometrium.

0682. **Uterus and Right Ovary**

Macroscopic: Specimen consists of an opened uterus and cervix measuring 7cm by 5cm by 3cm in A-P diameter with right fallopian tube 4cm in length by 1cm in diameter and right ovary 2cm in diameter. Two polyps, each 1cm in diameter are present in the fundus of the endometrium. The myometrium is normal and the cervix is slightly roughened. A-H Serial sections of cervix, clockwise from 12 o'clock. J.K Posterior slice L.Cornus M.Right adnexa, R.

Histology: There is extensive residual carcinoma in situ of the cervix, with glandular involvement. There are a few foci of microinvasion (Blocks D, F & G).

A focus of endometriosis is present in the cervix (Block E). The uterus is lined by inactive endometrium. At the fundus, there is an inactive hyperplastic polyp. The myometrium is normal. The ovary is inactive.

Uterus cervix and right ovary: **Residual carcinoma in situ with microinvasion.**
Inactive hyperplastic endometrial polyp.