The Anti-Cancer Council has convened a Working Party of these groups who have agreed to co-operate in the development of a central registry. In the first instance, all laboratories have agreed that a set of minimal data will be collected.

The participation costs of the private sector and public hospitals will be minimal as all major laboratories have computer facilities. Data will be transferred to the central registry via a modem. Access by these sectors to registry data will be via modem and print-out or by telephone. As a confidential safeguard, the laboratories will not have direct access through the use of VDU's. Rather, the laboratory will send via the modem basic identifying data for the women whose smears they receive. The Registry will return to the laboratory the known smear history of the women. The laboratory will complete the transaction by providing a coded cytology report. If the report was significantly abnormal, the registry will request follow up information at a later time. A minimal cost of approximately $500.00 per participating pathology laboratory will be required for software development.

SPECIFIC REQUIREMENTS FOR THE REGISTRY

Physical Location:

The registry will be housed on the same premises as the VC(G)S. The VC(G)S is currently located at the Prince Henry's Hospital in Melbourne. However, due to the anticipated re-location of Prince Henry's, the VC(G)S is currently reviewing its future location. The Health Department Victoria has undertaken to ensure that additional space is allocated to the Registry both in its present and future location.

Staffing:

The registry will require the following permanent staffing postions:

* 1 full-time epidemiologist
* 1 full time VDU operators
* 1 secretary/receptionist/VDU operator
* 1 full time medical record administrator

* sessional consulting statistician
* sessional software modification consultant.

The epidemiology position will be shared with the VC(G)S and the VC(G)S will provide full funding for that position.

Data Entry and Retrieval Procedures

Initially, data to be entered into the Registry data base includes:

Data from participating labs	VC(G)S
- Name/previous surname	Name/previous surname
- Birth date	Birth date
- Address	Address
- Date of smear receipt	Referring doctor
	Country of Birth
	Parity
	Hormonal status
	Contraception
	Symptoms
	Appearance of cervix
	Relevant past history (pelvic irradiation etc.)

Further developmental work to expand the data set will be carried out with participating laboratories. The Anti Cancer Council is currently facilitating these discussions.

VC(G)S data will be keyed directly into the data base from VC(G)S cytology request/report forms. Other pathology services have agreed to extract the above data and transfer it via modem to the registry. Mechanisms for promoting the transfer of data from public hospitals are being developed.

Direct access to data retrieval will be limited to the Registry. Private pathology services, general practitioners, public hospitals and other health care agencies will have access to information about the smears submitted by them only by request either through modem and printouts or by telephone.

Legal Issues and Confidentiality

Issues of confidentiality concern two broad areas, the first safeguarding the release of registry information and the second protecting the integrity of the registry from unlawful release.

Full confidentiality will be maintained through restricted access to the data. Modem transfer of reports and referring doctors will be by code. The Health Department Victoria, in co-operation with the Anti-Cancer Council of Victoria, is currently undertaking action to ensure that confidentiality is protected. Existing provisions under Section 61 of the Cancer Act appear to provide satisfactory safeguards at this time.

Follow Up and Recall Procedures:

Initially, the registry will seek follow-up information on all abnormal smears (colposcopy findings, histology reports etc) by:

Phase 1:

- contacting medical practitioners who referred their smears directly to the VC(G)S (this procedure is currently routine within the VC(G)S);

- contacting the participating pathology labs for abnormal smears reported to the registry.

Where the recommendation after an abnormal report was for further cytology, a reminder letter will be sent to the referring doctor three months after the date when the cytology report was due.

Phase 2:

The registry will seek to recall women who have already had a normal smear:

- Reminder letters will be sent to the referring medical practitioners at a defined time interval after the last normal smear;

- The VC(G)S currently recommends biennial (every two years) smears if the past history has been normal. This time interval may need to be adjusted if a different screening interval gains wide acceptance by the learned organisaitons (NH&MRC, Anti-Cancer Societies, Royal Australian College of Obstetricians and Gynaecologists etc.)

Phase 3:

The registry will seek to develop a call system for all eligible, unscreened women in Victoria if there is community and professional support for such an initiative.

BOARD OF MANAGEMENT:

The Registry will be overseen by an independent council or Board of Management. This body will be formally accountable for the management of the Registry to the HDV. An interim committee is being appointed by the Health Department Victoria to be responsible for the developmental stages of the Registry. Membership on the interim committee will include representation from:

- The Health Department Victoria
- The VC(G)S
- The Anti-Cancer Council of Victoria
- Private pathology services
- An epidemiologist
- A computer expert
- A gynaecologist/oncologist
- A general practitioner
- A lawyer
- 2 women's health consumers
- A family planning nurse nominated by the Women's Health Network
- A public hospital cyto-pathologist

Quality Assurance

Commitment to the introduction and maintenance of quality assurance mechanisms is regarded as essential to the effectiveness of the service.

The Board of Management will ensure the development of these mechanisms in line with recommendations arising from the National Strategy on Cervical Cancer Screening Services.

Evaluation

It is anticipated that the project will comply with the requirement of the National Strategy on Cervical Cancer Screening Services.

Funding Arrangements:

The costs of the establishment and the maintenance of the data base will be shared between the State of Victoria and the Commonwealth Government.

REQUIRED FUNDING:

STAGE 1

Establishment Costs

Hardware	$65,000	
Software	$ 7,500	
Software Modification	$10,000	
Equipment	$17,000	
	$99,500	$99,500

RECURRENT

Staffing

Epidemiologist	$52,000*	(already provided by VC(G)S)
2 Operators/Secretary/Rec.	$40,000	
Administrative Assistant	$23,000	
Software	$10,000	
Computer	$15,000	
	$88,000	$88,000

Operating Costs

Stationery	$ 3,000	
Computer Facilities	$10,000	
	$13,000	$13,000
	TOTAL	$200,000

STAGE 11 and 111

Costs for Stage 11 and 111 have not been estimated as further development will be dependent on progress at a national level.

COMMONWEALTH CONTRIBUTION

1987/88	$ 99,500
1988/89	$101,000

(It is noted that the substantial existing infrastructure and the salary of the epidemiologist are provided by the Victorian State Government.)

.....

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A member of the Australian Cancer Society
Director: Dr Nigel Gray A.M. MB, BS, FRACP, FRACMA

Anti-Cancer Council of Victoria

4 March 1988 CX-CRM-06/mr/1

Dear Nigel,

I write with the agenda for 30 March and details of the report of the Working Party on a Central Registry for Cervical Smears in Victoria. I enclose minutes of the original meeting with pathologists performing cervical cytopathology to discuss this concept as it contains those points which were agreed upon at the original meeting.

You will see that it was agreed that the VC(G)S should be the site for a central registry and that the VC(G)S Board or else a similar body at the VC(G)S should be constituted to control input and output of data from the Registry. It was agreed that pathologists are the people who should be supplying data to the Registry, and who should be having access to it.

The Registry was felt to be suitable to act as a reminder to pathologists or other medical practitioners of the follow up necessary after an abnormal report had been issued. It was also agreed that all relevant pathology from biopsies, hysterectomies where appropriate, and other surgery related to cervical dysplasia should be forwarded to link with previous smears in the Registry, just as it occurs now with the VC(G)S. It was also agreed that there should be linkage with the Victorian Cancer Registry to provide information on cancer of the cervix.

The final agreement at the original meeting was that pathologists would like to have feedback on their own statistics of smears performed and the outcome, particularly when persons had a cancer of the cervix diagnosed at a later date.

As you see from the report of the meeting on 29 September, it was felt necessary for further work on standardisation of reports and terminology, the manner in which computer facilities could be adapted to allow on-line access to a central Registry, and the confidentiality of information supplied to and from the Registry. A small working group has now addressed each of these areas and recommended the solutions below. I stress that these are recommendations only and I look forward to discussion of these points at the meeting on 30 March.

Report Codes for the Cytology Registry see attachment 2.

Adaptation of Computer Facilities for On-line Accesss see attachment 3.

The major benefit to participating laboratories will be a full knowledge of the relevant history of their patients at the time of generating their reports. The security within this proposed system is the non-interactive nature of Registry accession and in the controlled dial-back of registry-matched information to participating laboratories only.

A further safeguard against abuse of this system is the requirement for all enquiries from a given laboratory for information about a particular woman's

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(ignore fluorescent hi'lite)

smear history to be followed up within a given period by a report of the recent smear from that laboratory. If a report is not forthcoming within a given period, then the laboratory will be contacted by the Registry to explain a data enquiry without subsequent data entry.

Flow charts for recall and follow up of women with abnormal smears see attachment 4.

At this stage no follow up sequence has been developed for reminding women with a negative cytology report of the need for a smear at regular intervals.

Confidentiality of information

Opinion was sought on the legality of a pathologist reporting the results of a cervical smear to the central Registry. Under the present system, unless a medical practitioner has the signed consent of the women from whom the smear is taken, the result cannot be forwarded to a third party such as the proposed Registry without breaching confidentiality. As it was considered impractical to have 1.5 million women sign a consent form to allow reporting of the result to the Registry every two years, the members at the original meeting suggested that changing current legislation to make registration compulsory would free them from concern about breach of medical confidentiality. Our legal advisor confirmed that this is the case.

We have subsequently sought an opinion from the senior legal advisor of the Health Department of Victoria on the mechanisms required to legislate for compulsory registration. The Health Act is currently undergoing amendment. It was felt that it would be possible to amend the Cancer Act along the lines of registration of cancers for the Victorian Cancer Registry, bearing in mind the provisions in Section 61 relating to confidentiality of the information being supplied, stored in and allowed out of the Registry.

The legal advisor to the Department made it very clear that this legislation could only be introduced if there was agreement from both the practitioners supplying the information to and receiving information from the Registry, as well as representatives from women in the community from whom the smears were being taken.

Should be looked for women to opt out.

The Working Party recommends that legislation be introduced to make registration of both normal and abnormal cervical smears compulsory.

In summary, the recommendations of the Working Party above are put up for discussion by the users of this service. I would like to remind you that the primary aim in setting up a central Registry is to substantially improve the service available to women in Victoria. It should reduce the morbidity and mortality due to cancer of the cervix in both the short and long term.

I hope that the above recommendations are clear. I look forward to receiving any written comments that you may have for discussion at the meeting. I would appreciate any comment on the enclosed material at least one week before the meeting so that the time that we spend on 30 March will be productive.

Yours sincerely

Dr Robin Marks
Director of Programs

A member of the Australian Cancer Society
Director: Dr Nigel Gray A.M. MB, BS, FRACP, FRACMA

Anti-Cancer Council of Victoria

A meeting of the Working Party on a Central Registry of Cervical Smears will be held on Wednesday 30 March 1988 at 4 pm, at the Anti-Cancer Council of Victoria.

AGENDA

1. Welcome - Nigel Gray
2. Business
   a. Resume of recommendations
   b. Discussion
      i written comments
      ii any other comments
   c. Other business

CX-MRM-02/mr

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ATTACHMENT 1

Attachment 1

Report of the meeting of pathologists performing cervical cytopathology to discuss the central data base, 29 September 1987, at 4 pm at the Anti-Cancer Council of Victoria

Present: Chairman: Dr Robin Marks, ACCV
Dr Gabrielle Medley
Dr Robert Brown
Ms Sarah Gray
Prof W De Boer
Dr A Bodie
Dr DW Fortune
Dr R Davoren
Dr Heather Mitchell
Dr Graham Giles
Dr Nigel Gray
Dr D Stanisich
Ms Gillian Bettega

Apologies: Dr Michael Drake
Dr Peter Wallis
Dr Peter Thompson
Mr Ed Wilson
Dr Michael Traill

Minutes of the Meeting

Dr Nigel Gray welcomed those present and introduced the meeting by discussing the background of the setting up of the VC(G)S. Initially 95% of all smears went to the VC(G)S. This has reduced from that figure to 85% several years ago and is now 75%. The other 25% are either going to public hospitals or private pathology services.

Dr Gray explained that the VC(G)S in effect was acting as a centralised data base for many years. It is only recently since more smears have been going

elsewhere apart from the VC(G)S that we do not have a central registry of all smears performed in Victoria. The Chairman then led the discussion along the points on the agenda being:

1. Benefits to be gained by having a central registry
2. Ethical considerations and confidentiality involved in setting up a registry
3. Siting/Organisation/Control of the registry
4. Funding and interaction with Government
5. Sharing results from other pathology sources and Victorian Cancer Registry
6. Any other business

There was agreement of everybody present that there should be a central registry of Pap smears. A number of points were agreed on and others required further work. Those agreed on were:

1. Location

   It was agreed that the VC(G)S should be the site for a central registry as this is set up to do that right now.

2. Control

   The VC(G)S Board as currently constituted could be suitable to be the controlling council of a centralised data base. It is being looked at by a working party of the Health Department Victoria at present and modifications could be included to make the Board suitable to be nominated as the controlling body for the registry.

3. Access

   It was agreed that pathologists should be the people who have access to the screening histories of women in the registry.

4. Follow-up

   It was agreed that the registry could be used to remind pathologists of follow-up necessary for abnormal smears.

5. Other Pathology

It was agreed that all relevant pathology from biopsies, hysterectomies where appropriate, and other surgery should be forwarded to to link with previous smears in the registry.

6. Linkage

It was agreed that there should be linkage with the Victorian Cancer Registry which would provide information on cancers of the cervix.

7. Feedback

All the pathologists agreed that it would be useful to have feedback of a particular pathologist's own statistics of smears performed and outcome when persons had cancer of the cervix diagnosed. They should also have feedback of comparative data for other people but in an anonymous fashion. Quality control was felt to be an important outcome of this type of feedback.

It was suggested that further work was necessary on the manner in which legislation should be developed to allow pathologists to provide the central data base with results of these smears and also have access to previous smear histories on their clients. Other areas which required further work included: 1. the use of the registry to provide reminder notices for regular smears in women with normal smears; 2. standardisation on the amount of information on reports coming in to the registry; 3. standardisation of the terminology for use in reports; 4. the manner in which computer facilities can be adapted to allow on-line access to a centralised data base, as well as providing information from laboratories on-line.

Dr Heather Mitchell, being a member of the Australian Health Minister's Advisory Council on cervical cancer, reported that there was likely to be money available from the Commonwealth Government to set up a registry if an appropriate submission was made in the near future. This covered the area of funding. The total funding would be through Government, with both Commonwealth and State Government being involved.

A small working party comprising Ed Wilson, Ruth Davoren, Heather Mitchell,

Gabrielle Medley and Robin Marks will consider the unresolved areas requiring further work. This working group will then report back to a further meeting of all the interested parties prior to putting in a submission to the Commonwealth Government for funding of a registry for cervical smears.

The meeting concluded in a very optimistic manner following considerable agreement on the major areas of concern about establishment of a central data base for cervical smears in Victoria.

Robin Marks
October 1987
CX-MRM-01/mr

ATTACHMENT 2

Attachment 2

Suggested report codes for the cytology registry

The groupings of cytology reports for the Register will have to be fairly broad to encompass individual laboratory styles, there not being a uniform reporting system between laboratories within Victoria.

The following coding system in proposed:

000 UNSATISFACTORY

100 NORMAL - with endocervical cells
110 NORMAL - without endocervical cells

200 BENIGN CHANGES

309 HPV INFECTION ALONE

400 CIN 1 - without HPV
409 CIN 1 - with HPV
410 CIN 2 - without HPV
419 CIN 2 - with HPV
420 CIN 3 - without HPV
429 CIN 3 - with HPV
430 CIN ENDOCERVICAL - without HPV
439 CIN ENDOCERVICAL - with HPV

500 SUSPICIOUS OF INVASIVE CANCER (LESION AT LEAST CIN) - without HPV
509 SUSPICIOUS OF INVASIVE CANCER (LESION AT LEAST CIN) - with HPV

600 INVASIVE CANCER OF CERVIX - squamous without HPV
609 INVASIVE CANCER OF CERVIX - squamous with HPV
610 INVASIVE CANCER OF CERVIX - adeno without HPV
619 INVASIVE CANCER OF CERVIX - adeno with HPV
620 INVASIVE CANCER OF CERVIX - adenosquamous without HPV
629 INVASIVE CANCER OF CERVIX - adenosquamous with HPV

630 INVASIVE CANCER OF CERVIX - other

700 INVASIVE CANCER OF ORGANS OTHER THAN CERVIX (eg endometrium)

800 INCONCLUSIVE - abnormal cells not suggestive of invasive cancer, but with another feature preventing accurate assessment, eg infection, inflammation, scanty specimen

810 INCONCLUSIVE - abnormal cells possibly suggestive of invasive cancer, eg for use when it is not possible to distinguish between an active cervicitis and invasive cancer.

NOTE: The digit 9 in column 3 indicates that the report commented on cytological evidence of HPV infection.

ATTACHMENT 3

Attachment 3

Proposed computer facilities for on-line data accession

Overview

It is proposed that the Registry will provide to all participating laboratories a microcomputer and modem and software to facilitate the input of data to the Registry and allow participating laboratories to enquire of the central data base. This microcomputer will be configured in order that its function be dedicated to application relevant to the Registry and further it would remain the property of the Registry.

The microcomputer/modem would enable participating laboratories to register smear requests and obtain a relevant history from the Registry's data base.

Patient matching will be totally controlled by the Registry's computer with the Registry staff validating near-matches.

Participating laboratories will be called back via the modem link to receive relevant history details on Registry matched patients.

Participating laboratories will advise the Registry of the result of the current investigation, again using the micro/modem.

As a consequence of their participation, participating laboratories, if they so wish, will receive a range of data summaries relevant to their own performance, subsequent results on their own patients and comparable data for the State of Victoria. Such information will be sent by the Registry to participating laboratories at regular intervals. Only the recipient's data will be identified in each report. The comparable data from other laboratories will not allow identification of individual laboratories.

Proposed Method of Operation

The micro computer provided to participating laboratories will have a 'burnt-in' menu which will allow the following:

1. Input new smear data from the keyboard.

2. Accept new smear data from in-house computer.
3. Send new smear data to Registry.
4. Access Registry response.
5. Input smear result data via keyboard.
6. Input smear result data from in-house computer.
7. Send result data to Registry.

This range of options would be handled as follows:

1. Input New Smear Data from Keyboard

For participating laboratories who are not computerised or who elect manual entry, this menu option will lead to a screen prompt enquiry seeking:

Patient's Surname and previous Surname,
Patient's Given Names,
Patient's Address,
Patient's Date of Birth,
Patient's Parity (if known),
Requesting Doctor,
Laboratory Reference Number.

This data will be held within the microcomputer until the laboratory elects to send a batch of such data to the Registry for registration and enquiry.

2. Accept New Smear Data from in-house Computer

Those laboratories with amenable in-house computers could down-load the data referred to above by modification of their worksheet generating software or the development of application-specific software. The down-loaded data would be held and handled as above.

3. Send New Smear Data to Registry

When invoking this menu option the software would initiate connection to the Registry and the transfer of data accumulated from 1 to 2 above. After sending this data, the call would be terminated.

The Registry computer, on receipt of a batch of new smear data from a participating laboratory, will search for matching

patients. Data relating to matches will be accumulated in a despatch file. 'Near-matches' will be brought to the attention of the Registry staff who will accept or reject matching to a uniform standard based on their experience. Any matches elected by them would be added to the despatch file. On completion of the matching process, the Registry computer system would return the call to the participating laboratory and down-load the relevant patient histories.

A log of these enquiries will be held in the Registry computer against the participating laboratory to ensure that results are subsequently received and to protect against inappropriate enquiry.

4. Access Registry Response

Under this menu option the participating laboratory could display and/or print responses from Registry as above.

5. Input Smear Result Data via Keyboard

Under this menu option the software in the microcomputer should facilitate the addition of a 3 character numeric response against records held from 1 or 2 above. These responses would be held and accumulated for subsequent despatch to the Registry.

6. Input Smear Result Data from in-house Computer

Some participating laboratories may elect to down-load this data from their in-house computers. Data would be transferred and handled similarly to 2 above. Because of the brevity of this data requirement, computer interfacing for this function is probably not necessary.

7. Send Result Data to Registry

When invoking this menu option the software would initiate connection to the Registry and the transfer of data accumulated from 5 and 6 above.

On receipt of smear result data, patient records within the Registry system will be updated, including the setting of follow-up

flags. As data is received from a participating laboratory, the enquiry log referred to above will be updated. If no result is recorded agianst an enquiry logged under 3 above within a week, the Registry will contact the participating laboratory.

ATTACHMENT 4

Attachment 4

Suggested Sequence for Recall and Follow-up of Women with an Abnormal Smears

1. Abnormal report with further investigations recommended

Time*	Seek follow-up info. from
3 months	Laboratory
6 months	Practitioner
9 months	Practitioner
12 months	? Woman

* Timed from data of abnormal cytology report

2. Abnormal report with recommendation for repeat cytology

Time*	Reminder letter to
3 months	Practitioner
6 months	Practitioner
9 months	Practitioner
12 months	? Women

* Timed from data repeat cytology recommended

3. Reminder letter for further cytology after treatment for an abnormality

Time*	Reminder letter to
6 months	Practitioner
9 months	Practitioner
12 months	? Women

* Timed from date of treatment.

CX-RRM-02/mr
2 March 1988

flags. As data is received from a participating laboratory, the enquiry log referred to above will be updated. If no result is recorded agianst an enquiry logged under 3 above within a week, the Registry will contact the participating laboratory.

A member of the Australian Cancer Society
Director: Dr Nigel Gray A.M. MB, BS, FRACP, FRACMA

Anti-Cancer Council of Victoria

29 February 1988

Cervical mtg

CX-CRM-02/mr/1

Dr Nigel Gray
Director
Anti-Cancer Council of Victoria

Dear Nigel

You will recall that a small working group of the Anti-Cancer Council of Victoria has been looking at the requirements necessary to establish a central registry of cervical smears. This followed an initial meeting of cytopathologists and others with an interest in cervical cancer in which it was agreed that a registry of some form was desirable.

The Working Group has now agreed on a set of recommendations. We would like to discuss these with all the persons who have an interest in the area. Accordingly, I am writing to invite you, or your representative to attend a meeting at the Anti-Cancer Council of Victoria on Wednesday 30 March from 4-6 pm.

I shall be sending a document with the full details of the recommendations in the next week. I would be pleased if you could read them and forward to me any points which you feel need clarification at least a week prior to 30 March. There will be quite a large number of people at the meeting, and the only way we can have useful discussion is by careful preparation beforehand.

We think that the proposal for a central registry of cervical smears is an important step forward in the attempt to reduce the morbidity and mortality due to cervical cancer in Victorian women. We look forward to your participation in establishing it.

Yours sincerely

Dr Robin Marks
Director of Programs

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Report of an Anti-Cancer Council of Victoria Working Party on Recommendations for the Screening Interval to Prevent Carcinoma of the Cervix

A working party of the Anti-Cancer Council of Victoria was convened to consider the policy of the Council on recommendations for screening interval to prevent carcinoma of the cervix. This followed rejection by the VCOG of the recommendations of the National Consensus Conference on Screening Interval for Carcinoma of the Cervix. The working party comprised:

G Giles
H Mitchell
M Quinn
D Reading
R Rome
coopted: W Chanen
convener: R Marks

The current Anti-Cancer Council of Victoria recommendation for screening interval is two years for women who have had sexual intercourse. The working party considered this interval in light of concerns expressed by gynaecologists that:-

1. There is an increased incidence of dysplasia and invasive carcinoma of the cervix in young women in recent years;

2. There is a new disease of rapidly invasive carcinoma of the cervix in young women in recent years.

There was considerable discussion to both the concerns of the gynaecologists. It was agreed that there was insufficient epidemiological data on hand at present to confirm or deny these propositions. Therefore the working party was faced with several options:-

Option 1

That we maintain the status quo, ie, continue to promote two yearly screening.

Option 2

That we change the recommendation to annual smears until the age of 35 years then three yearly if previous smears have been normal.

Option 3

That the current recommendation be changed to recommend three yearly screening for all women.

All these options were considered on the agreement that research should be undertaken to obtain data which would determine whether or not one or both of the areas of concern of the gynaecologists was true. The recommendations were then to be reassessed, and changed if necessary, once satisfactory data were available.

The working party then agreed on the following recommendations:-

1. Cervical screening is recommended only for women who have had sexual intercourse. The screening should start within three years of first intercourse.

2. Screening can cease at the age of 65 years if previous regular smears up until this age have been normal. This does not imply that women should not continue to be seen regularly by a doctor after the age of 65 years to exclude other gynaecological disorders.

3. The screening interval for all women with normal smears should remain at two years for the time being.

4. Research should be undertaken to determine whether or not there is (1) an increased incidence of invasive carcinoma of the cervix in young women; (2) there is a new disease of rapidly invasive carcinoma of the cervix in young women.

5. The recommendations on the screening interval should be reassessed, and altered if necessary, when the results of the research recommended in 4. are available.

Attachment 1

Research necessary to determine whether there is an increased incidence of invasive carcinoma of the cervix in young women in recent years.

This research should be able to be undertaken on existing Australian data. Registration of incident cases of invasive carcinoma of the cervix has been organised in each state and territory since 1982. At present, data is not available from each state beyond 1983.

There is a need to complete the registration of all new cases of carcinoma of the cervix in each Cancer Registry up until the end of 1988. These data can then be pooled and time trends by age groups can be analysed over the last 7 years. Even though data collection in NSW and SA started earlier, the information gathered since 1982 should be sufficient to determine whether or not there has been any real change in the incidence of invasive carcinoma in various age groups.

Research necessary to determine whether there is a new disease of rapidly invasive carcinoma of the cervix in young women in recent years

PROBLEM: THE RESCREENING INTERVAL BETWEEN PAP SMEARS

The Consensus Conference of July 1988 recommended a rescreening interval of 3 years, if 2 previous smears were negative. There is concern among clinicians that this policy disadvantages younger women among whom they believe there to be high rates of precursor disease and a rapid onset type of cancer.

The following facts about cervical cancer are known:

1) Cervical cancer is subject to secular trends.

2) An increase in the incidence and mortality has been noted in younger women (<35 yrs) in the U.K. See Appendix 1.

3) Incidence figures have only been collected in Australia since 1982 and therefore trends cannot be interpreted. Mortality data for Australia show a decline in death rates among younger women except for the age group 30-34 years. See Appendix 2.

4) Women aged <35 years accounted for
   22% of incident cases in 1982 (n=182)
   7% of the deaths in 1986 (n=20)

The issue of current concern is whether there is an age difference in the protection derived from negative cervical cytology, and if so, whether the difference is of sufficient magnitude to justify a short rescreening interval.

In 1986, the IARC published a major collaborative study of the protection derived from negative cytology. The study primarily focused on women over 35 years of age who had been screened in centrally organised programmes in the 1960s-1970s and who developed cancer in the 1960s-1980s. The IARC concluded there was no evidence of an age differential in the protection conferred by negative cytology. This conclusion has been criticised on the grounds that information was available on only a very small number of women aged less than 35 years, and that the time period when the women developed cancer was prior to recent concern over rapid onset cancer.

The possibility of undertaking a similar multicentre case-control study across all age-groups in Australia was explored in 1985-86 and was not considered feasible, primarily because of the difficulties associated with compiling and confirming comprehensive lifetime screening histories of women with cancer - more than 200 laboratories have reported on Pap smears in Australia and most do not have computerised records.

Analyses within the Victorian Cytology (Gynaecological) Service over the period 1980-1985 indicates that while numerically more interval cancers occur among older women, the rate of interval cancer diagnosis is higher in younger women. This is the first population-based evidence of an age differential in interval cancer diagnosis rate. (This research has been submitted for publication). It is the first study to evaluate the rate of cancer diagnosis among sufficient numbers of screened younger women during a period when clinicians consider the problem of rapid onset cancer has been apparent.

Before basing public health policy on these findings, the following two conditions should be met:

1) The VCGS research should be accepted for publication in a refereed journal.

2) The findings should be confirmed in another setting. A confirmatory study would require:

   (a) Identification of a large group of women who have been screened negative (approx. 500,000) during a recent time period when the problem of rapid onset cancer was considered to be apparent (ie. since 1980).

   (b) Over the next 3 years, calculation of the OBSERVED rate of squamous cell carcinoma diagnosis among the screened group via relevant Cancer Registries. (3 years is selected as it represents the longest currently recommended rescreening interval).

   (c) Determination of the EXPECTED rate of cancer diagnosis by applying the appropriate IARC rates to the screened group.

   (d) Record linkage within participating laboratories. The ability to record link subsequent negative smears within participating laboratories so that each woman contributes to the calculations of the observed and expected number of cancers only in relation to her most recent screening within the 3 years of interest is essential.

This study could be undertaken in a large overseas laboratory (eg. British Columbia) or possibly within 2 or 3 large computerised Australian laboratories. In this latter situation, the cost of the study would depend heavily on the state of the records in the participating laboratories.

TABLE I

Registrations of Cancer of the Cervix in England and Wales

Rates per Million

Age Group

Year	15-24	25-34	35-44	45-54	55-64	65+
1963-65	3	53	301	394	336	301
1966-68	4	58	273	432	340	295
1969-71	7	73	201	389	333	273
1972-74	8	88	165	335	363	276
1975-77	10	107	170	293	373	274
1978-80	12	135	196	230	345	267
1981-83	10	160	217	211	313	260

From: Office of Population Censuses and Surveys, 1986

TABLE II

Deaths from Cancer of the Cervix in England and Wales

Rates per Million

Age Group

Year	15-24	25-34	35-44	45-54	55-64	65+
1950-52	0.6	18	74	180	300	337
1953-55	0.7	23	76	163	253	316
1956-58	0.7	24	90	163	235	318
1959-61	0.5	19	100	172	204	306
1962-64	0.5	11	103	184	193	286
1965-67	0.5	11	92	189	195	260
1968-70	1.4	11	69	189	200	247
1971-73	1.3	13	57	176	201	224
1974-76	2.1	18	46	140	208	216
1977-79	0.8	24	59	124	197	215
1980-82	2.2	30	62	100	176	203
1983-85	1.0	34	63	95	160	194

From: Office of Population Censuses and Surveys, 1986

From the UK Intercollegiate Working Party on Cervical Cytology Screening Report (Nov 1987)

APPENDIX 2. From data presented at the Consensus Conference by Bruce Armstrong

Mortality data for 1975-79 and 1980-84, together with previously unpublished data for 1985-86, are shown in more detail in Table 2. These data show that, except in the age group 30-34 years, there were no further increases in mortality from cancer of the cervix in those under 45 years of age in 1985-86. Mortality continued to fall in those 45 to 54 years of age

TABLE 2: RECENT TRENDS IN MORTALITY FROM CANCER OF THE CERVIX IN AUSTRALIA

	AVERAGE DEATHS/YEAR			MORTALITY RATE/100,000		
AGE	1975-79	1980-84	1985-86	1975-79	1980-84	1985-86
<20	0.0	0.0	0.0	0.0	0.0	0.0
20-24	1.8	0.4	1.0	0.31	0.06	0.15
25-29	6.4	6.6	6.0	1.11	1.07	0.91
30-34	9.3	12.6	16.0	1.94	2.08	2.54
35-39	11.6	15.4	16.5	2.78	2.94	2.69
40-44	13.4	19.8	22.5	3.61	4.69	4.64
45-49	25.0	23.4	22.5	6.70	6.36	5.57
50-54	38.0	28.0	25.5	10.07	7.52	7.10
55-59	42.6	36.2	37.0	12.66	9.73	9.94
60-64	46.8	42.6	42.0	15.59	12.84	11.48
65-69	40.8	46.0	52.0	16.04	15.98	17.44
70-74	37.6	34.8	38.5	19.44	14.88	14.74
75-79	32.0	30.6	26.5	22.48	18.84	14.16
80-84	25.8	22.6	25.0	28.24	20.79	21.38
>84	18.2	18.8	27.0	30.75	25.95	29.58
All	349.8	337.8	358.0	4.04	3.53	3.44

26 JUL 1988

Draft report. Please comment, correct and return to me please

AUSTRALIAN CANCER SOCIETY

REPORT OF CONCENSUS CONFERENCE ON CERVICAL CANCER SCREENING

MELBOURNE 22 JULY 1988.

Jill Chrous 26 JUL 1988

Introduction.

With the financial assistance of the Australian Department of Community Services and Health a conference of representatives of Commonwealth, State and Territory Health Departments, Cancer Councils, Royal Colleges, together with professional and community groups was held to arrive at screening recommendations using the Pap. smear, based on epidemiology, pathology, practicality and ethical considerations. The aim was to end the confusion caused by the varied existing recommendations. What was required was a statement to guide health providers and consumers and to give health educators throughout Australia a simple uniform message to present to all Australian women and to assist the development of an achievable national cervical cancer screening program.

It was emphasised that cervical cancer screening was unique in that it was an example of true prevention detecting premalignant lesions rather than invasive cancer, and women must be reassured that the object of the Pap. smear is not to detect cancer but to prevent it.

Australian data has shown that:

1000 women develop cancer of the cervix each year.

350 women die from cervical cancer each year.

60% of women at risk remain unscreened.

75% of women who develop cancer of the cervix have never been screened.

Recommendations

1. Women who have not had a Pap. smear should be the first priority group for cervical cancer screening programs.

2. All women should be held to be at risk because an exclusive high risk group cannot be identified.

3. Screening should commence at 18 years.

4. Screening should stop at 65 years providing 3 normal smears have been recorded in the previous 10 years.

5. Accepting that there would be a greater relative protection with more frequent screens, providing 2 annual smears are normal, subsequent 3 yearly screening is acceptable.

These recommendations do not apply to the follow-up of those women who have had an abnormal smear.

They are made on the understanding that the screening interval is but one element of an integrated screening program. A comprehensive program must provide a choice of screening providers and venues, an acceptable framework for recruitment, recall and registration of data for evaluation, widespread public and professional education, laboratory and reporting quality assurance, research to address the motivational factors that can improve women's utilisation of screening services, together with adequate treatment of detected abnormalities and their follow-up. Funding will be required to test many of these activities to determine the most efficient use of resources and to develop the most effective program.

Clinicians throughout Australia are recognising a rise in the incidence of precursor lesions of cervical cancer, particularly in young women, but a significant rise in the incidence of invasive cancer is not being reflected in the cancer registry data. The incidence of interval cancer between screenings is low in this group. However this clinical development warrants close monitoring to ensure that the recommendations remain appropriate, but the evidence available now to support the adoption of the 3 yearly screening cycle for women under 35 years of age, as well as for the older group is most persuasive.

W.Brian Fleming
Chairman, Patient Affairs Committee
Australian Cancer Society.

THE NEW SOUTH WALES STATE
RESEARCH • EDUCATION • TREATMENT
CANCER COUNCIL

copy to Brian Fleming and Dr Rodger Pepperell

17th July, 1985

Dr. Nigel Gray
Director
Anti-Cancer Council of Victoria
1 Rathdowne Street
CARLTON SOUTH 3053

Dear Nigel,

Thank you for your reply to our letter.

We are very interested in the approach you have taken in relation to mammography and breast cancer. The national consensus group appears an excellent way of getting all the interested parties together.

The idea of a similar meeting on cervical cancer was disucssed at our last Working Party meeting. I am sure you are aware that we are participating in the national collaborative study of cervical cancer and screening being co-ordinated by Bruce Armstrong. We felt that a national consensus meeting early next year would be a useful way of publicising the national study as well as getting together the interested groups.

I will be discussing the idea with Gordon Sarfaty but I agree that ACS would be the appropriate organisation to sponsor a national meeting. I have received a letter from Brian Fleming giving details of the "breast summit" (!) and expressing strong interest in a similar meeting in cervical cancer. I shall be writing to Brian Fleming after my disucssion with Gordon and hopefully we can begin the necessary planning.

Thank you for your interest and assistance and we will definitely keep in touch.

Yours sincerely,

Malcolm Coppleson MD, FRCOG, FRACOG
Head, Gynaecological Oncology Unit
King George V Hospital, Sydney
Chairman, Working Party on Cervical Cancer

Dr BRIAN FLEMING

MR. W. BRIAN FLEMING
M.S., F.R.C.S. (ENG.), F.R.A.C.S., F.A.C.S.

347 5144

PRIVATE CONSULTING SUITE,
THE ROYAL MELBOURNE HOSPITAL,
P.O. 3050, VICTORIA.

5th February, 1985

Dr.Nigel Gray,
The Anti-Cancer Council of Victoria,
1 Rathdowne Street,
Carlton. 3053

Dear Nigel,

re: Cervical cytology screening

Please find enclosed a copy of a letter Laurie Wright has sent to the N.H., & M.R.C. This points out the problems. I think perhaps we should wait to see what the Maternal Health Committee of the N.H., M.R.C., organize. I would not be at all surprised if they organize a consensus conference. If they do not, then I think we should get together as we have done with breast cancer.

Kind regards,

Yours sincerely,

W.B.Fleming.

Encl.

c.c. Mr.Laurence Wright.

With the Compliments of . . .

LAWRENCE WRIGHT
Executive Director

CER SOCIETY INC.
rner King and Castlereagh Streets, Sydney, N.S.W.
one (02) 231 3355. Telegraphic address: Austcancer Sydney

ıen, AK, GCMG, GCVO, KBE, KStJ
FACS

THE AUSTRALIAN CANCER SOCIETY INC.
Box 4708, G.P.O. Sydney,
N.S.W. 2001 Phone (02) 231 3355

29 January 1985

The Secretary,
Maternal Health Committee,
National Health & Medical Research Council,
P O Box 100,
WODEN, ACT, 2606.

Dear Madam,

Thank you for the invitation to respond further to the recommendation made by your Council at its 97th session on cervical cytology.

In our letter B111/5 dated 4 December we conveyed the reservations held by clinicians regarding the recommendations and since then have attempted to determine a consensus view that would be supported by clinicians, epidemiologists and public health officials. Sadly, but perhaps not surprisingly, this consensus has not been achieved. The issue is of importance to this Society as we have in final draft, a set of guidelines to general practitioners which will advise on appropriate cancer checks. These guidelines are to be published in the Medical Journal of Australia and will, when published, give a comprehensive guide to the medical profession which is, at present, lacking. One component of the guidelines is the recommendations regarding cervical cytology and we regard it as essential that these should not conflict with those issued by your committee.

In the discussions which have gone on since our letter of 4 December we have reached agreement with the clinicians that an appropriate statement would be:

> 'Cervical smears should commence once a patient begins to have sexual intercourse and should be performed annually thereafter'.

However whilst this meets the needs of clinicians and avoids any prospect of neglect it may not be justifiable on an epidemiological basis. The argument is put that the frequency of smears should be determined not only by the criteria of earliest possible detection but also on whether this earlier detection then leads to lower mortality or less treatment. There appears to be, at this time, insufficient data to resolve this question.

Later this year the Anti-Cancer Council of Victoria is to compare statistics from the Victorian Cancer Registry and the Victorian Cytology Service to see if any guidance is available from such a study.

It is now our opinion that any statement on cervical cytology should be deferred and that a conference be arranged once the Victorian study is completed to see if, in the light of its findings, a consensus view emerges. This Society would be pleased to participate, or if requested, arrange such a conference.

With best wishes,

Yours sincerely,

L.A. Wright
Executive Director

245/85

NEWS RELEASE

FROM THE
AUSTRALIAN MINISTER FOR HEALTH
THE HON. NEAL BLEWETT

COMMONWEALTH GOVERNMENT PROVIDES $1.5 MILLION FOR AIDS RESEARCH

The Commonwealth Minister for Health, Dr Neal Blewett, today announced details of the Commonwealth Government's $1.5 million program for research into AIDS during 1986.

"The research will cover the scientific, medical and social aspects of the disease", Dr Blewett said.

"Australia is a world leader in adopting preventive health measures to reduce the spread of AIDS. These research projects are vital to Australia maintaining a positive and co-operative approach to control of the disease".

Research grants applied in four main areas:

1. A special virology unit will be established in Melbourne, under the direction of Associate Professor Ian Gust, of Fairfield Hospital. The unit will conduct research and co-ordinate the work of other research institutions throughout Australia on virology including the development of methods for viral detection and virus analysis and the monitoring of drug trials.

2. An epidemiology and clinical unit will be established in Sydney under the direction of Dr David Cooper, of St Vincent's Hospital. It will initiate and co-ordinate studies into epidemiological and clinical aspects of the disease and assist in clinical trials.

Note: The two special units (virology in Melbourne and epidemiology in Sydney) will receive estimated total funding of $900,000 in 1986.

3. Approximately $100,000 has been set aside for clinical trials that are to be conducted in Australia in the near future.

2/...

4. Grants have been made to individual researchers in five States - New South Wales, Victoria, Queensland, South Australia and Western Australia. Further grants are under consideration.

Dr Blewett said funding details for the special virology and epidemiology units and for the clinical trials had yet to be finalised. The approximate grants to individual researchers are included in the attached list.

CANBERRA
13 December 1985

NSW GRANTS

Dr P. Gatenby, RPAH, Sydney
'HTLV III and HBV probing in AIDS and related conditions'

$39 304

Dr P. Gatenby, RPAH, Sydney
'Immunological and psychosocial aspects of AIDS in patients with haemophilia'

$10 000

Prof. J. Dwyer, Prince of Wales Hospital
'Experimental approaches to the management of AIDS'

$15 000

Prof. R. Connell, Department of Sociology, Macquarie University
'Social aspects of response to AIDS - Study A'

$56 071

Sydney AIDS Study Group, A/Prof R. Penny, St Vincents Hospital, University of NSW
'Endothelium in Kaposi's Sarcoma'

$20 000

Dr D. Wakefield, St Vincents Hospital and Prince of Wales Hospital,
'Ocular manifestations of AIDS'

$10 000

* Dr A.L. Cunningham, Westmead Hospital, Sydney
'AIDS: perinatal infection, strain variation and molecular epidemiology of the virus'

$78 448

* to be incorporated within the Special Unit for Virology when established.

VICTORIAN GRANTS

Dr M. Barnett, Department of Pathology and Immunology, Monash University
'Prognostic indicators for the development of AIDS or related indicators in haemophiliacs'

$35 000

Dr B.E. Kemp, Repatriation General Hospital, University of Melbourne
'Development of specific antisera to synthetic HTLV III peptides'

$40 745

Dr M.S. Sandrin/N.J. Deacon, Department of Pathology, University of Melbourne
'Characterisation of the TA antigen as the HTLV III receptor'

$28 953

Dr J.P. Coghlan, Howard Florey Institute, University of Melbourne
'Location of AIDS virus expression using hybridisation histochemistry'

$53 088

Dr I. Goller, Victorian Health Department
'Prospective study of psychosocial factors influencing HTLV III/LAV infection in Vic. homo/bisexual men'

$10 000

Dr I. Denham, Melbourne Communicable Diseases Centre
'Risk factors and transmission of HTLV III virus in intravenous drug users'

$1 641

'Risk factors and transmission of HTLV III virus in prostitutes'

$1 641

* Dr J. Denham, Prof. I. Gust, Fairfield Hospital, Melbourne
'HTLV III culture in seronegative persons at high risk'

$59 030

* Dr R.R. Doherty, Fairfield Hospital, Melbourne
'Virological studies and clinical trials of antiviral agents in HTLV III infection'

$158 029

* to be incorporated within the Special Unit for Virology when established.

QUEENSLAND GRANTS

Dr I. Frazer, Princess Alexandra Hospital, Qld
'HTLV III virus and papilloma virus as cofactors in rectal carcinoma in situ'

$23 000

* Dr J. Pope, QIMR, Brisbane
'Analysis of auto-immune reactions in AIDS patients'

$31 604

* to be incorporated within the Special Unit for Virology when established.

SOUTH AUSTRALIAN GRANTS

Dr M. Ross, SA Health Commission
'Assessment of AIDS risks and the cognitive informational and behavioural components of AIDS'

$83 398

Dr C.J. Burrell, IMVS, Adelaide
'Detection and significance of HTLV III replication in antibody positive individuals'

$90 253

Prof. M.A. Vadas, IMVS, Adelaide
'Development and clinical application of monoclonal antibodies against HTLV III env antigens'

$54 748

* to be incorporated within the Special Unit for Virology when established.

WEST AUSTRALIAN GRANTS

A/Prof. R.L. Dawkins, Royal Perth Hospital,
University of W.A.
'Comprehensive care and investigation of AIDS in W.A.'

$28 000

THE AUSTRALIAN Wednesday September 16 1987 P6(Supp)

$5 million for cancer studies

THE Federal Government is to spend more than $5 million in the next three years on evaluating tests for the early detection of breast cancer and cervical cancer.

The Minister for Community Services and Health, Dr Blewett, said yesterday the object of the trials would be to determine whether well co-ordinated, high quality screening services could be made available nationally to women at risk from these cancers.

LEADING ARTICLES

Puzzling changes in cervical cancer in young women

It is the talk of the gynaecological oncology world — both national and international — that young women with cervical cancer are faring poorly. Early signals that the mortality rate was rising appeared in the literature some years ago in reference to populations in the United Kingdom,[1,2] New Zealand,[3] and the United States.[4] Indeed, the reports included a previous one from Armstrong and Holman[5] an update paper from whom appears in this issue of the Journal (page 410). Since then evidence (not all in agreement) is accumulating that the following changes seem to be occurring: speeding up of the precancerous phases;[6-8] an increasing incidence of the disease;[9,10] alterations in the histological patterns of the disease;[10,11] more aggressive primary lesions;[11,12] earlier lymph node involvement;[10] earlier local and distant failures after treatment,[11] especially with stage-I disease (unpublished observations); and poorer survival.[11,13]

While this description would fit the Australian scene — both by anecdote and by a series that we have collected from a major Sydney teaching hospital (unpublished observations)[10] — the updated report by Holman and Armstrong confirms the rise in mortality in women aged 30–39 years that was noted in their 1981 paper, but now demonstrates a downturn in the mortality in both cohorts of younger women in the age groups 20–24 years and 25–29 years. In a previous leading article, Armstrong wrote of "The falling, rising incidence of invasive cancer of the cervix".[14] His comment on the present study might well refer to the "rising, falling incidence". However, the authors point out that the latest downturn has occurred on the basis of only 13 deaths in the two cohorts in the period, 1980–1984, that they chose to survey, and that the explanation for this fall is uncertain. Such a finding is in stark contrast to the aggressive behaviour of the disease that was seen in younger women between 1981 and 1986 in the Sydney survey that has already been cited (unpublished observations).[10]

The question on the minds of many authorities obviously is: what is happening? What underlies the advent of all this discussion on the varying mortality rates? Our perplexity increases as we reflect that it would have been comforting to expect, this late in the century, after close to four decades of Papanicolaou screening with its attendant cost and effort, some real downturn in mortality rates as a reward. The anguish becomes more acute when we note that where smear campaigns have been the most comprehensive, such as in Canada, an upswing in mortality in young women is now occurring in at least three provinces.[15]

In attempting to answer these questions concerning the mortality and the associated change in virulence of the developed disease in young women, two themes stand out: the efficacy of the Papanicolaou smear test and the strong possibility that a virus is involved. We can persist with our belief that the smear technique is as effective as was originally thought, with the qualification that the reason for the changed mortality pattern is simply due to failure to reach the most at-risk groups. This idea, which is at least 20 years old, has wide appeal and there is published evidence to show that there is much skewing in the distribution of women who attend smear programmes.[16] Holman and Armstrong favour increased attention to groups of specific age in the matter of smear programme policy. The theory that the intensity of the whole pattern change in the disease is such that the mortality figures in the young (the most heavily screened group of all) would be higher were it not for the efficiency of the smear test and that, in a sense, the use of the smear technique is holding the lid on an explosive situation would be in line with the expected efficiency of the smear-test.

The second theme concerns the entry of viruses, more especially papillomavirus (wart virus) onto the scene — a discovery now nearly 10 years old. This discovery was preceded in the early 1970s by a far more widespread acceptance of a yet older idea that the original cervical focus might be associated with similar disease elsewhere in the lower genital tract and perineal region.[17] Indeed, the field concept resulted from the clinical experience of the increasing multicentricity of lesions, which is now especially evident in precursor lesions. In view of such a qualitative change, the time was right for the consideration of the début of a new neoplastic process whose presentation was more like that of an infection. The subsequent fate of the viral theory of lower genital tract carcinogenesis has been remarkable. Aided by some elegant techniques of immunochemistry and nucleic acid hybridization, it is now possible to state that over 80% of cancer and precursor lesions contain the hallmarks of papillomavirus infection.[18]

Currently cytological and colposcopic studies reveal a virtual epidemic of a new lesion — subclinical papillomavirus infection.[19] Until 1977 these macroscopically invisible "flat warts" on the cervix were unknown.[20] It was not long before subclinical papillomavirus infection was linked with cervical preneoplasia.[21] This, in turn, is associated with a change in distribution which tends towards an increasing incidence in and the involvement of younger age groups.[2,22] Evidence on the same points for vaginal and vulvar preneoplasia is also available. Vulvar preneoplasia is regarded traditionally as a disease of postmenopausal women; however, the bulk of patients with vulvar preneoplasia is now much younger.[23] Lesions tend to be non-keratinized and are associated with papillomavirus infection rather than are keratinized on a background of vulvar dystrophy as in the classic case. So remarkable are these differences as to suggest that we might be dealing with two different disorders, each with their own aetiology and natural history.

Such a discovery is altering rapidly our considerations of the nature of lower genital tract cancer as a class of venereal disease. This, of course, opens up many conceptual avenues for reflection on the cause of the changed epidemiology. To an extent, it releases us from sole dependence on the vicissitudes of the outcome of smear programmes as an explanation for mortality rates which have so characterized the position since the 1960s.

In view of the resounding appearance of a virus on the scene, our editorial would be deficient if it were not to contain some reflection as to whether aspects of viral behaviour may lie behind the kind of pattern that we are beginning to recognize, be it apparent or real. Has there been a change in the host-parasite relationship over about a decade, a change in what we might call the quality of carcinogenesis of the genital tract?

The advent of rapid changes in sexual mores almost throughout the Western world, and the increased spatial mobility of susceptible populations are well known topics of discussion. It was suggested several years ago that the upsurge in venereally-transmitted disease would predict a commensurate upswing in the number of women who were at risk of developing cancer of the lower genital tract.[24] Perhaps the early age of commencing intercourse and the existence of "high-risk" male consorts contribute to this incidence.[25,26] On the other hand, an increase in the incidence of cancer of the cervix coupled with the aggressive disease that is associated with rapidly-developing lesions in multiple sites are more reasonably interpreted through alterations in the qualities of the carcinogenic process, which could include the virus itself.

Variations of viral virulence of an episodic character are well known. They are usually assigned to mutations in the viral genetic apparatus whose origin in turn is dubbed "spontaneous". These may be obvious because of their abruptness, as in the past pandemics of influenza virus, or more insidious as in the case of lower genital tract

carcinogenesis. In the present circumstances when viral behaviour is being monitored continuously by the activities of scores of laboratories, it is possible to sense secular variations in viral virulence, as are currently thought to be occurring with another virus with a sexual mode of transmission, the human immunodeficiency virus, perhaps from the same basic cause.

Perhaps the act of frequent sexual passage streamlines the recruitment and subsequent synthesis of the virus from its cellular precursors, while at the same time it refines its ability to attack the lower genital tract more extensively than the cervical region, as well as its efficiency as a cell-transforming agent.[27] The passaging of organisms which is attended by enhanced virulence is a phenomenon that is well recognized in microbiology. It seems that, in future, given the pace of the accumulation of knowledge, it will be difficult to contain the source of these variations within the concept of "spontaneous" viral mutations as we ascertain exactly what is happening to the virus when it passes from one host to the next.

If the tailoring that comes from passage can elevate a virus to a "supercarcinogen", there may be a conceptual place for the alternative of a more moderate carcinogen such as one or more of the viral building-blocks themselves. Some of these are now recognized as oncogenes,[27] although it is unlikely that, by their permanent intracellular habitat[28] and other considerations, they are fitted to maintain either the genital tract spread or the pace of carcinogenesis of their ultimate derivative, the whole virus. Mazur and Cloud's recent comment is apposite: "the ultimate influence of human papilloma virus on the evolution of cervical intraepithelial neoplasia is not yet known".[29]

We should persist with experiments not only to detail events in the life of the viral particle that are affected by frequent spatial exposure between hosts[30] but also to show that the virus itself may be a small, albeit very powerful, offshoot of the interaction of sperm with cervical tissue.[31] In other words, the same neoplastic process could vary in rate or quality according to the efficiency of the molecular mechanisms that are involved — virus, particle or precursor protein — in a given case or over a given time.

MALCOLM COPPLESON
PETER ELLIOTT
Visiting Medical Officers
Gynaecological Oncology Department
King George V Memorial Hospital for Mothers and Babies, Sydney
BEVAN L. REID
Reader, Department of Obstetrics and Gynaecology, The University of Sydney

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Strokes and hypertension — the effect of treatment

Physicians who are experienced in the introduction of new therapies know well that three phases are usually involved.[1] Initially, the therapy is the answer to the problem — "the greatest thing since sliced bread". Thus, the therapy is embraced with enthusiasm. Then side-effects and failures are observed increasingly, and the pendulum swings in the opposite direction — "terrible stuff, wouldn't give it to my mother-in-law". Consequently, the therapy falls rapidly from favour. Lastly, in more rigorously defined circumstances, and with a knowledge of its drawbacks, the therapy is reintroduced and finds its real place in the physician's armamentarium.

We seem to be seeing this sequence in the treatment of mild to moderate hypertension. The last decade has seen major advances in our knowledge of the treatment of hypertension. Large multicentre studies have demonstrated that the treatment of hypertension reduces significantly its mortality and morbidity, principally from strokes.[2-4]

Importantly, at least one study has also studied specifically the over 60 years of age group and has, in general, produced the same results.[5] The results of these major studies have been well promulgated and discussed, in this Journal[6] as well as in others,[7] and have led to a deservedly widespread enthusiasm for the treatment of hypertension, that is, we have negotiated the first phase.

In this issue of the Journal (page 412) the onset of the second phase can be seen; eight cases of focal cerebral ischaemia and infarction that were presumed secondary to antihypertensive therapy are described from Perth, and the authors warn that "overtreatment" of hypertension may actually cause strokes. (It should be noted that a similar series of patients has also been described in Canberra,[8] so the problem is not an isolated one.)

So, how far back should the pendulum swing, and are we in danger of overreacting and possibly losing the undoubted benefits that are associated over all with the treatment of hypertension? There are clues in the report of Hankey and Gubbay which, coupled with a knowledge of the pathophysiology of cerebral blood flow and of stroke, the pharmacology of the commonly used antihypertensive drugs, and the details of the published trials, should enable us to halt the pendulum in the correct place.

It has long been recognized that the abrupt

SUN Living

The ignorance about cancer

By DAN McDONNELL

THERE is always something more chilling about a disease that claims the lives of young adults, especially if children are left behind.

To know that many of those deaths could have been avoided by providing more information to those at risk makes it even more harrowing.

There is little doubt that such is the case with cervical cancer, a disease which claimed 334 Australian lives in 1984.

A new survey of young people has found a disturbing ignorance about cervical cancer despite an increase in deaths from the disease in Australian women under 35.

Sydney University obstetrics and gynaecology lecturer Dr Suzanne Abraham, who conducted the study, wants more education about the cancer and the papilloma or wart virus with which it is believed to be linked.

Dr Abraham says this will have to happen if cervical cancer is to be considered a sexually-transmitted epidemic, as many experts have labelled it.

She found that among 100 people interviewed aged between 17 and 26 few knew of the apparent predisposing factors which led to development of the virus and onset of the cancer.

Those factors include starting sex at an early age, having a high number of sexual partners and having partners at high risk of carrying the virus.

Some reserchers believe there is also a link with the contraceptive pill and smoking.

Interviewed late last year in a typical Sydney suburb, only four per cent of the young men and women were able to reply that cervical cancer was caused by a virus, infection or "germ."

Most simply said they did not know how the cancer developed.

Only 22 per cent mentioned that the cancer might be related to sex, multiple sexual partners, early age at first intercourse or to an infected partner.

The Pill was cited as a possible cause by 14 per cent, stress by 13 per cent and smoking by four per cent.

Other factors raised by the interviewees included drug abuse, miscarriage, abortion, irregular periods, sex during menstruation, diet, poor health and genes.

> In spite of the number of young people who associated cancer of the cervix with sexual behavior, only four per cent of them considered it to be a sexually-transmitted disease.

"In spite of the number of young people who associated cancer of the cervix with sexual behavior, only four per cent considered it to be a sexually-transmitted disease and 15 per cent felt that a condom or diaphragm would help in prevention," Dr Abraham said in a recent letter to *The Medical Journal of Australia*.

"The findings indicate a lack of knowledge among young people, 80 per cent of whom will have experienced sexual intercourse.

"If papilloma virus and cervical cancer are to be considered a sexually-transmitted disease of epidemic proportions, it is imperative that accurate and simple information is available."

Dr Abraham said the incidence of pap virus and cervical cancer in young women were increasing as was the evidence that the two were linked.

While the overall rate of cervical cancer has declined, there has been a rising death rate among Australian, British and American women under 35.

Although a connection between the pap virus and genital herpes has now been widely dismissed researchers believe they have proved a link with the sexually-transmitted genital warts, a disease curable only through surgery.

Latest figures estimate pap virus is appearing in four to five per cent of smear tests on women from Victoria and NSW.

Dr Abraham said last week she thought women should ask for regular pap smear tests. But she acknowledged there was now a debate about cost-effectiveness of undergoing the tests every 12 months or every three years.

Prominent Sydney gynaecologist Dr Malcolm Coppleson has highlighted the limtations in accuracy of the pap smear test in a recent paper on the issue.

However he is cautious of claims that the tests are being performed too regularly at too high a cost.

He thinks it could be contended that screening programs are holding down a prospective leap in cervical cancer created by the "behavioral revolution."

The Australian Cancer Society advises annual cancer smears. The National Health and Medical Research Council and the Royal Australian College of Obstetricians and Gynaecologists favor 12-monthly tests only for high-risk groups.

The NHMRC recommends three and two-yearly checks for women not deemed to be at high risk.

A recent Queensland study found that of 211 women aged 40 and below who were diagnosed as having cervical cancer fewer than 50 per cent had ever undergone a smear test.

An earlier WA study produced an even more depressing result. It found that only 39 per cent of cervical cancer sufferers questioned had sought the test.

Said Dr Coppleson:"Not only do those at risk often fail to heed the considerable propaganda that is broadcast, but the rescreeening of the more zealous who do take heed is, with limited resources, costly and counterproductive..."

"In the final analysis, the problem is in balancing the health dollar against the value of a life saved."

PAGE
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9-10-86

Sex can transmit cancer: professor

By BILL BIRNBAUER,
medical reporter

Cervical cancer could be classified as a sexually transmitted disease because of its link with the human papilloma virus, Professor Derek Llewellyn-Jones said last night.

Professor Llewellyn-Jones said recent research had found a strong association between the virus, also known as wart virus, and the development of abnormalities in the cervix which could progress to cancer. The genital wart virus was spread by sexual intercourse.

Professor Llewellyn-Jones, who is the chairman of the Better Health Commission, said detection of abnormal cervical cells by regular Pap smear screening could prevent a quarter of the cases of cervical cancer and the earlier diagnosis could prevent about one third of the deaths.

At present only about 30 per cent of Australian women have had a single Pap smear. But the trend to annual screening of all sexually active women raised important financial and social questions, Professor Llewellyn-Jones said.

He said the cost of implementing annual cervical smears for the 3.5 million sexually active women in Australia would be at least $169 million. The cost of detecting one case of cervical cancer was $100,000.

At present most women having regular smears were from higher socio-economic groups which seemed least likely to develop cervical cancer.

Professor Llewellyn-Jones said the prevention of illness did not attract the millions of dollars spent each year researching the biology and treatment of cancer. To date, the research effort had been a failure. "Any significant reduction in cancer prevalence and mortality will be made only if prevention is funded," he said. "It is essential that prevention receive a high priority in future research programs."

Professor Llewellyn-Jones was speaking at the annual general meeting of the Peter MacCallum Hospital.

AGE
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Cervix cancer epidemic feared

LONDON, 7 Oct — A new, virulent form of cancer of the cervix could cause the death toll among sexually active women to shoot up by 70 per cent, doctors warned today.

The British Medical Association said that over the past 10 years there had been an epidemic of the pre-cancerous form of the disease, largely among young women.

One computer model was now predicting a 70 per cent increase in mortality in women under 50 in 10 years' time. That would take the death toll in Britain from the present 580 to 1000 a year in that age group.

The BMA report said: "There is some evidence that cervical cancer in the younger woman is more aggressive. It is not yet possible to determine whether this is true because of the different hormonal status of the pre-menopausal women, or whether we are seeing a new and more virulent variant of the cancer which is initially present in the sexually more active part of the population."

The report, drawn up by the BMA's board of science, criticises the "poor record" on screening women in Britain for the early pre-malignant signs of the disease, when the cure rate is virtually 100 per cent. "Sixty per cent of women with cervical cancer have never been screened," it says.

The report calls for the interval between normal smears to be cut from five to three years, starting in younger women instead of concentrating on women over 35. Screening of younger women was more likely to result in prevention of the disease rather than detection of a cancer with only a 50 per cent cure rate.

—Reuter

AGE
PAGE 14
24-4-86

Cancer check

from B. Scoullar

On returning to Australia after 11 years abroad I am appalled at the lack of facilities for the simple routine PAP smear test all women are encouraged to have, particularly those over 40 years of age.

When TB was a killer the Government set up free routine checks; but cervical cancer, which is also a killer, has been given no such treatment. I do not want to jump to conclusions, but I cannot help wondering, "is it because it is a woman's problem?"

The Government should use some of the 1 per cent health levy for cancer prevention by setting up a similar service using qualified doctors and nurses to travel to selected areas where women, who were previously notified of their appointment time, date, and place, could be screened.

BARBARA SCOULLAR,
Corio.

Smear test

AGE APL 29 '86

from Dr N. Gray, director, Anti-Cancer Council of Victoria

I hasten to reassure Barbara Scoullar (24/4) concerning the pap smear program. Any Victorian woman can have a pap smear simply by asking her family doctor to do it. This service is funded by Medicare. If the specimen is sent to the Victorian Cytology (Gynaecological) Service (as are 85 per cent) then a first class service is provided free of charge at State Government expense.

We encourage Victorian women to have pap smears. Although only 250,000 of the "at risk" population of 1.4 million have never had a pap smear, this group experiences the majority of the cervical cancer. Cervical cancer is a completely controllable disease if the pap smear is used correctly.

(Dr) NIGEL GRAY,
Melbourne.

differences; or in evaluating competing interpretations of the data on differential access to general practice by social class. She is careful to confine herself to comparative studies in demonstrating the universality of inequality within Europe. She avoids simple, unifactorial explanations of inequalities: her conclusion that "socio-economic circumstances play the major part in subsequent health" acknowledges both the substantial evidence on health-damaging behaviour and the equally powerful case that "living and working conditions can impose severe restrictions on an individual's ability to choose a healthy lifestyle". Her account of the major developments in surrogate (especially census-based) health data reinforces the case she makes for collecting real data via a National Health Survey, like those in North America. Here, as in most other areas where Black made recommendations, Whitehead sees "a lack of action, particularly at national and central level". But she is impressed by the many local statutory and voluntary responses to the increasing child poverty, deteriorating housing stock, and uncoordinated policies that have contributed to inequality in the 1980s. Local authorities have made an especially strong contribution in each of the priority areas identified in the Black report, improving life for children and disabled people and encouraging preventive and educational action for better health.

Scandinavia provides the best examples of how public policy can improve health—eg, Norway's national food and nutrition policy and the Finnish experience of reorientation toward primary health care (using carrots rather than sticks). Britain, it seems, must make do with extra-parliamentary action: along with the local authorities, Whitehead cites as examples of good practice the Church of England report on urban priority areas,[11] the WHO Healthy Cities Project, and pressure groups ranging from the British Medical Association and the HEC itself to the newly formed Public Health Alliance.[12] Her assessment of their contribution rings equally true for her report: "Together, these initiatives are helping to keep the issue of health inequalities firmly on the agenda".

HUMAN PAPILLOMAVIRUSES AND CERVICAL CANCER: A FRESH LOOK AT THE EVIDENCE

THE strong association between sexual activity and cervical cancer has encouraged the search for a sexually transmissible agent that could initiate or promote cervical neoplasia.[1] Spirochaetes, spermatozoa, smegma, *Trichomonas vaginalis, Chlamydia trachomatis,* and herpes simplex virus type 2 have all come under suspicion, but proof of carcinogenesis has been lacking in every case. Ten years ago, it was noted that there was a strong association between human papillomavirus (HPV) infection and cervical cancer and a carcinogenic role was postulated for specific papillomavirus types in the genital tract; we summarised the evidence in an editorial in 1985.[2]

DNA hybridisation studies of tumour tissue and cervical cancer cell-lines showed that most genital cancers harbour a specific HPV type.[3] Types 16 and 18 are found in 40–70% of invasive cancers and in several cervical cancer cell-lines. A further 10–20% of genital cancers contain DNA sequences homologous with HPV 11, 31, 33, 35, or other untyped HPVs. Analysis of the transcriptional pattern of HPV 16 and HPV 18 shows that there is a difference in the state of the viral DNA in benign and malignant tissue. Integration of HPV DNA into the genome of the host cell has been observed only in invasive cancers and in cervical cancer cell-lines, whereas in benign and premalignant lesions the HPV DNA is extrachromosomal.[3,4] In all cell-lines analysed so far, integration of HPV DNA involves specific regions of the viral genome, leaving the E6 and E7 open reading frames (ORFs) intact. The protein products of the E6 and E7 ORFs have now been demonstrated in several cervical cancer cell-lines containing HPV 16 or HPV 18 DNA.[5] Although the function of the E6 and E7 gene products in cultured cervical cancer cells is unknown, the analogous E6 product of the bovine papillomaviruses has a transforming function. If these early papillomavirus proteins are present in human tumour cells in vivo as well as in vitro it will undoubtedly strengthen the argument in favour of an aetiological role for the viruses.

Nevertheless, there is a need for caution in the interpretation of these data. Although HPV DNA can be demonstrated in 80% of cervical cancers, several groups, including Dr Meanwell and colleagues in this issue (p 703), have shown that the distribution is heterogeneous.[6–8] Even in tumours with a high number of gene copies per cell, the viral DNA may be present in only a subset of keratinising carcinoma cells and expressed as mRNA in only a proportion of the HPV 16 positive biopsy specimens studied.[8] These findings cast doubts on claims for tumour monoclonality and are not entirely consistent with an oncogenic role for the viruses. Moreover, genuine integration of viral DNA in the cancer cell chromosomes is less common than has been suggested and concatemeric forms are seen.

The high prevalence of papillomavirus infection in women with cytologically and colposcopically normal cervices casts further doubt on the oncogenic role of these viruses. A report from South Africa documents the highest rate of cervical papillomavirus infection worldwide.[9] Viral

11. Archbishop of Canterbury's Commission on Urban Priority Areas. Faith in the city: a call for action by church and nation. London: Church House Publishing, 1985.
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3. Gissmann L, Schwarz E. Persistence and expression of human papillomavirus DNA in genital cancer. In: Evered D, Clark S, eds. Papillomaviruses. Ciba Foundation symposium 120. Chichester: Wiley, 1986: 190–207.
4. Durst M, Kleinheinz A, Holz M, Gissmann L. The physical state of human papillomavirus type 16 DNA in benign and malignant genital tumours. *J Gen Virol* 1985; 66: 1515–22.
5. Seedorf K, Oltersdorf T, Krämmer G, Röwenkamp W. Identification of early proteins of the human papillomaviruses type 16 (HPV 16) and type 18 (HPV 18) in cervical carcinoma cells. *EMBO J* 1987; 6: 139–44.
6. McCance DJ, Kalache A, Ashdown K, et al. Human papillomavirus types 16 and 18 in carcinomas of the penis from Brazil. *Int J Cancer* 1986; 37: 55–59.
7. MacDougall JK, Beckmann AM, Kiviat NB. Methods for diagnosing papillomavirus infection. In: Evered D, Clark S, eds. Papillomaviruses. Ciba Foundation symposium 120. Chichester: Wiley, 1986: 86–103.
8. Lehn H, Krieg T, Sauer G. Papillomavirus genomes in human cervical tumours: analysis of their transcriptional activity. *Proc Natl Acad Sci USA* 1985; 82: 5540–44.
9. Markowitz S, Leiman G, Margolios KA. Human papillomavirus and cervical intraepithelial neoplasia in an African population. *S Afr J Epidemiol Infect* 1986; 1: 65–69.

changes were found in 66% of black African women, who have a very high risk of cervical cancer but also a very high frequency of all venereal diseases. Wickenden et al[10] showed that the frequency of HPV was also high in women who had been successfully treated for carcinoma-in-situ (CIN) by laser therapy: 48% of these women with cytologically and colposcopically normal cervices were found to harbour HPV DNA, often in high copy number, several years after therapy and without any evidence of recurrence of CIN. The high frequency of the virus in the normal cervix has been taken to indicate that other events are needed to initiate the carcinogenic process.

In order to explain the discrepancy between the large number of normal individuals with latent papillomavirus infection and the small number of genital cancers in the population, zur Hausen suggested a mechanism of failing intracellular control of persisting viral genomes in proliferating cells that leads to development of the tumour in a few individuals.[11] This model of carcinogenesis also explains the long interval between the primary infection and the appearance of the tumours. However, until the mechanism of gene control has been more clearly defined, it would be unwise to assume that the genital papillomaviruses are aetiological factors for cervical cancer. It is especially important to keep an open mind since Meanwell and co-workers indicate that the association between HPV and cervical cancer may be age-related, and the apparent rise in frequency of HPV 16 DNA positivity with severity of disease may be an effect of increasing age. This suggestion merits closer consideration; clearly future studies of the prevalence of the viruses in normal women and cervical cancer patients should be controlled for age.

The uncertainty surrounding the role of the papillomaviruses in the cervix has presented problems for clinicians who have to decide whether to treat anxious patients (male and female) who fear they may be harbouring an oncogenic virus. Gynaecologists and venereologists are keen to know whether there is sufficient evidence to deduce that human papillomaviruses are the sexually transmitted carcinogen we have been seeking for so many years; or whether, once again, we have to conclude that the biological significance of an association between a sexually transmitted agent and cervical cancer cannot be explained. In this respect the paper by Meanwell and colleagues is reassuring. The case against the papillomaviruses is far from proven; aggressive treatment of genital warts, which cause little discomfort and may regress spontaneously, can scarcely be justified.

ASSESSING RESPIRATORY DISABLEMENT

A DIMINUTION in lung function impairs the capacity for exercise; the term respiratory impairment can describe both aspects. However, modern usage identifies respiratory *impairment* with loss of lung function, respiratory *disablement* with reduced exercise capacity, and respiratory *handicap* with the social disadvantage.[1] The disablement is then independent of aptitude and external circumstances but related to the lung function and factors that influence motivation.

The principal symptom, breathlessness on exertion,[2] may have a psychological component, but is commonly due to airflow limitation or increased exercise ventilation. The traditional method of assessment was for the physician to accompany the patient on a walk, hence the more recent 12 or 6 min walking distance test of McGavin and colleagues.[3] The associated clinical interview had earlier led Fletcher to define clinical grades of breathlessness,[4] and subsequently these grades were added to[5] and the criteria were extended.[6] Further quantification was provided by the visual analogue scale of breathlessness.[7] The scale is a 10 cm line representing the continuum from not breathless to very, very breathless; the patient indicates the point on the line which he judges to represent his sensation. The scale is better for depicting changes in breathlessness than the absolute level. An early physiological approach to quantification was the dyspnoeic index, which represents the association between breathlessness and loss of ventilatory reserve. The index is the ventilation at maximal exercise ($\dot{V}_E$max) expressed as a percentage of the maximal breathing capacity,[8] the latter usually derived from the forced expiratory volume in one second (FEV_1). The derivation neglected inspiratory flow limitation.[9] In addition, the calculation assumed a proportional relation between $\dot{V}_E$ max and FEV_1 which is not observed in practice.[10-12] Neither form of breathlessness score was of great help for assessing disablement. Instead, until lately, the Pneumoconiosis Medical Panels (now the Medical Boarding Centres for Respiratory Diseases) were well served by clinical judgment and measurements of FEV_1. However, assessment is more difficult in patients with multiple underlying disorders. There have also been cases of misrepresentation of the degree of breathlessness by some applicants for compensation, and calls by lawyers for what may be unrealistically precise assessments. Such considerations have dictated a more objective approach.

The primary abnormality is loss of lung function; a method of describing the impairment accurately should also define the physiological component of exercise limitation. In practice, few lung function tests were widely available and both the American Thoracic Society (ATS) and the European Society for Clinical Respiratory Physiology have largely confined themselves to FEV_1, forced vital capacity (FVC), the ratio index FEV_1/FVC (FEV_1%), and transfer

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HPV 16 DNA IN NORMAL AND MALIGNANT CERVICAL EPITHELIUM: IMPLICATIONS FOR THE AETIOLOGY AND BEHAVIOUR OF CERVICAL NEOPLASIA

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Summary Southern blot hybridisation showed that cervical cancer biopsy specimens from 31 of 47 (66%, 95% confidence interval [CI] 52–80%) patients contained HPV 16 homologous DNA sequences, with evidence of integration of viral genome into host cell chromosomes in 7. Normal ectocervical biopsies from 9 of 26 (35%, 95% CI 16–53%) control women contained HPV 16 DNA, and none showed evidence of integration. HPV 16 DNA positivity did not correlate with marital or sexual history, parity, use of oral contraceptives, or smoking habits in cases or controls, or with outcome of treatment in cases. HPV 16 DNA positivity was found less frequently with age <40 years old than with age >40 in both cases ($p<0.05$) and controls ($p<0.01$). After age-adjustment there was no significant difference between cases and controls in frequency with which HPV 16 DNA was found. These data suggest that the association between HPV 16 and cervical neoplasia is age-mediated and that the presence of the viral genome may not always warrant intervention.

Introduction

DESCRIPTIVE and analytical epidemiological studies indicate that sexual transmission of an infectious agent may be important in the aetiology of cervical cancer.[1,2] Human papillomaviruses (HPV) have been discussed as possible candidates for a number of years. Papillomaviruses have oncogenic potential in animals,[3] and there have been several reports of malignant transformation of benign HPV-induced lesions in man.[4] Cytological, histological, and immunohistochemical studies reveal an association of HPV with cervical neoplasia[5-7] and deoxyribonucleic acid (DNA) cloning and hybridisation techniques[8] have so far demonstrated the association between seven HPV genotypes (6, 11, 16, 18, 31, 33, 35) and intraepithelial and invasive cervical lesions.[9-15] HPV types 6 and 11 are associated predominantly with genital warts and low-grade dysplasias,[10] whereas HPV 16 and 18 are found in few premalignant cervical lesions[16,17] but in the majority of invasive cervical carcinomas, depending on the geographical source of material.[11,16-19] Integration of HPV 16 DNA into the host genome has been observed only in high-grade dysplastic and malignant cervical tissue.[20,21] In addition, transformation of NIH 3T3 cells by a recombinant HPV 16 plasmid and by a genomic DNA sample from cervical cancer tissue containing HPV 16 has been observed in vitro.[22,23] The mechanism of HPV 16 DNA-associated cell transformation requires clarification; nevertheless the data cited above support the view that the presence and integration of HPV type 16 is a risk factor for the development of cervical cancer.[16]

Early reports indicated that HPV 16 DNA was rarely found in normal cervical epithelium.[24] Although more

TABLE I—CHARACTERISTICS OF CASE AND CONTROL GROUPS

Variables	Cases (n=47)	Controls (n=26)	Test of equality of groups U	χ^2	p
Continuous					
Median age (year)	49	39	322·0	..	<0·001
Median parity	2	2	553·5	..	0·494
Discrete					
Marital history					
Ever married	47	20	..	11·8	<0·001
Married before 20 years old	18	8	..	0·414	0·520
Coital age*					
Onset before 17 years	19	12	..	0·217	0·641
Onset before 20 years	33	17	..	0·244	0·636
More than 1 sexual partner	34	19	..	0·005	0·946
Oral contraceptives ever used (combined pill all cases)	12	10	..	1·330	0·249
Ever smoked	21	14	..	0·56	0·453
Non-Caucasian	1	1	..	0·00†	1·000†

*Uncertain history in 2 cases and in 1 control.
†Yates' corrected values.

recent studies indicate that HPV 16 DNA may be recovered from 8·6–35% of normal cervical epithelia,[25,26] the frequencies with which HPV 16 DNA occurred in normal and malignant cervical tissues have not been compared. Furthermore, although HPV infection has been implicated as a contributor to possible alterations in the behaviour of cervical neoplasia in women under 40 years of age,[25,27,28] the age-specific frequency of association and implications of HPV 16 infection in normal or malignant cervical epithelia have not been investigated. We aimed therefore (1) to determine the frequency with which HPV 16 DNA could be isolated from normal and malignant cervical biopsy specimens taken from women living in the West Midlands region, (2) to determine the physical state of the HPV 16 DNA in biopsy specimens, and (3) to investigate the relation between HPV 16 and several disease and demographic characteristics.

Subjects and Methods

Subjects (Table I)

The case-group comprised 47 previously untreated patients with invasive cervical cancer referred to the Queen Elizabeth Hospital, Birmingham, between March, 1984, and March, 1985, for radiotherapy. All patients were staged according to FIGO (International Federation of Obstetrics and Gynaecology) criteria and tumour dimensions were recorded. Patients were treated with intrauterine/intravaginal radium sources (mean dose to 'Point A' 51·7 [SEM 2·65] Gy in 1–2 [mean, 1·3, SEM 0·06] fractions), followed by external whole pelvis X-irradiation with central shielding (mean dose to pelvic sidewall 37·9 [SEM 0·89] Gy in 17 [SEM 0·67] fractions). 18 patients subsequently underwent extended total hysterectomy and bilateral salpingo-oophorectomy. Patients were assessed for response at 6 weeks and then every 3–4 months after treatment. Objective response and duration of response and survival were defined according to World Health Organisation criteria.[29]

The control group comprised 26 consecutive women being treated at the Birmingham and Midlands Hospital for Women for benign gynaecological disorders and who gave informed consent for cervical biopsy. Clinical, cytological, and histological histories were obtained from the case-notes and by interview of each control subject.

Methods

Colposcopy-directed biopsy specimens of normal original squamous epithelium were taken from controls and tissue with the macroscopic appearance of invasive cervical cancer was taken from cases (biopsy size 40–80 mm³). Samples were immediately snap frozen and stored in liquid nitrogen. Cryostat-cut sections were taken from each biopsy specimen for histological assessment and DNA analyses were done without knowledge of the type of material under investigation. DNA extraction, restriction enzyme cleavage, Southern blotting,[30] and high (T_m −9°C), moderate (T_m −22°C), or low (T_m −45°C) stringency hybridisations were done with methods similar to those described before.[26] For this study, *Pst*I (multicut enzyme for HPV 16), *Bam*HI (single cut enzyme for HPV 16), and *Hin*dIII (no-cut enzyme for HPV 16)[23] restriction endonucleases were used.

TABLE II—FREQUENCY OF FINDING HPV 16 DNA IN CASES AND CONTROLS

—	HPV 16 DNA positive	HPV 16 DNA negative	Total
Cases			
Large-cell keratinising carcinoma	3	4	7
Large-cell non-keratinising carcinoma	20	9	29
Small-cell squamous carcinoma	4	2	6
Adenosquamous cell carcinoma	2	0	2
Well-differentiated adenocarcinoma	2	1	3
Total cases	31	16	47
% frequency (95% confidence interval)	65·9 (52–80)	34·1	..
*Controls**			
Group A	5	8	13
Group B	0	3	3
Group C	1	3	4
Group D	3	3	6
Total controls	17	9	26
% frequency (95% confidence interval)	34·6 (16–53)	65·4	..
Overall total	33	40	73

*Group A—no clinical history of genital warts or neoplasia with normal 5-year smear history and normal current cytology and colposcopy; group B—no clinical history of genital warts or neoplasia with unknown 5-year smear history and normal current cytology and colposcopy; Group C—clinical history of genital warts or neoplasia but with normal 5-year smear history and normal current cytology and colposcopy; group D—current cytological dyskaryosis or histological CIN or koilocytosis.

Results

Incidence, Amplification, and Physical State of HPV 16 DNA

At high stringency, HPV 16 DNA was found in invasive carcinoma biopsy specimens from 31 of the 47 cases (66%, with 95% CI = 52–80%) and in normal ectocervical biopsy specimens from 9 of the 26 controls (35%, with 95% CI = 16–53%) ($\chi^2_1 = 6·64$, $p = 0·01$) (table II). Controls were younger and less likely to be married than were cases (table I).

Multiple carcinoma biopsy specimens from 12 cases were examined. 3 showed evidence of a heterogeneous distribution of HPV 16 DNA, since both positive and negative findings were obtained from adjacent areas of the same tumour. Estimates from reconstruction experiments indicated that as few as one HPV 16 DNA sequence could be detected per host haploid genome. The median copy number, ascertained in 26 of 31 carcinomas positive for HPV 16, was 75 (range 1–250) gene copies per host genome (gc/hg). Other HPV genotypes were not detected by low or moderate stringency hybridisation. In 24 of 31 positive carcinomas *Pst*I restriction enzyme analysis indicated that HPV 16 DNA occurred as episomal molecules (fig 1). DNA from 13 of these 24 cases were also analysed with *Bam*HI

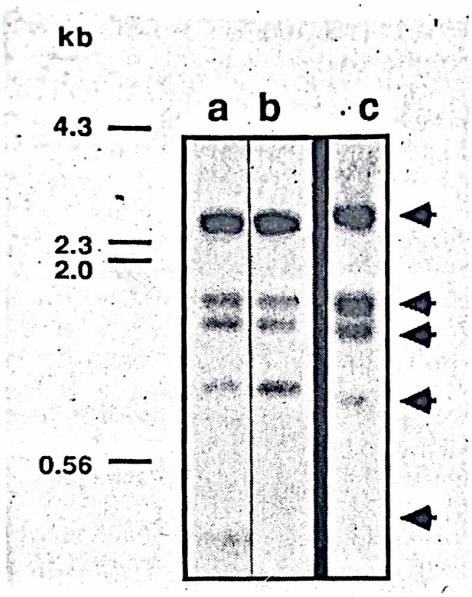

Fig 1—*Pst*I digests of DNA extracted from (a) normal cervix, (b) well-differentiated adenocarcinoma of cervix, and (c) large-cell non-keratinising squamous-cell carcinoma of the cervix, hybridised to ^{32}P-labelled HPV 16 DNA insert at high stringency (T_m-9°C).

Prototype *Pst*I restriction pattern indicated by arrows. Lambda *Hin*dIII size markers indicated by bars.

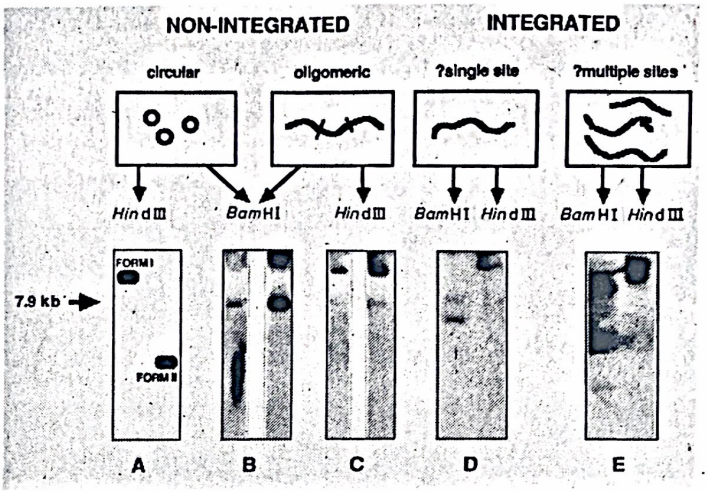

Fig 2—Determination of the physical state of HPV 16 DNA in cervix biopsies.

HPV 16 DNA is a double-stranded, circular molecule which may exist with both strands covalently closed to form a superhelical twist (form I), with one single stranded nick to form a relaxed or open circle (form II), in oligomeric (head-to-tail repeat) form, or integrated into the host cell genome.[3]

If HPV 16 DNA is present in either of the circular forms or as oligomeric molecules, then cleavage with *Hin*dIII restriction enzyme (which does not cleave HPV 16 DNA) produces the banding pattern seen in (A) or (C), respectively.

If the HPV 16 DNA is integrated into the host cell genome, then *Hin*dIII cleavage produces a high molecular weight band (D) which is similar to that seen with oligomeric HPV 16 (C). To discriminate between these oligomeric and integrated forms, further cleavage of duplicate DNA samples with *Bam*HI restriction enzyme (which cleaves HPV 16 at a single site) is required.

If there is no integration then *Bam*HI cleavage yields a linear HPV 16 DNA molecule which migrates with the 7·9 kb marker as in column (B). If integration has occurred (and provided HPV 16 DNA is not integrated at its *Bam*HI site), then *Bam*HI cleavage usually yields 2 bands as seen in column (D); the size of these 2 fragments is determined by the relative locations of *Bam*HI sites within the HPV 16 DNA and flanking host-cell DNA. The *Bam*HI and *Hin*dIII patterns seen in E suggest that integration has occurred at multiple host genome sites.

and *Hin*dIII restriction enzymes. In all 13 HPV 16 DNA was present in concatemeric ("head-to-tail" repeat) form. 7 of 31 positive cases showed evidence of HPV 16 DNA integration into host cell chromosomes (fig 2).

The median copy number, ascertained in 8 of 9 HPV 16 positive controls, was 50 gc/hg (range 1–200). In all positive controls, *Pst*I analyses yielded restriction patterns that were identical to those obtained with prototype HPV 16 DNA, with no evidence of viral DNA integration into host cell chromosomes (fig 1).

Comparisons between Cases Positive and Those Negative for HPV 16

There was no significant difference between HPV 16 negative and positive cases in terms of patients' marital or sexual history, menopausal status, parity, use of oral contraceptives, or smoking habits. There was no evidence to suggest that HPV 16 was more frequently associated with any histological type or grade of tumour. The frequency of finding HPV 16 in cases increased with tumour size and stage, but neither trend reached conventional levels of statistical significance (χ^2_1 [linear trend] for size = 0·8, p = 0·37; χ^2_1 [linear trend] for stage = 2·4, p = 0·12) (tables II and III).

Treatment was similar for cases whether the tumours were positive or negative for HPV 16 (table III). 42 of the 47 cases showed a complete clinical and radiological response to treatment, 4 showed a partial response, and 1 was static. The median follow-up for this group was 20·5 months. Patients who responded completely had a significantly better survival than those who did not (χ^2_1 [Mantel-Cox] = 6·74, p < 0·01), but there was no significant difference in duration of response (χ^2_1 [Mantel Cox] = 0·05, p = 0·83) or survival (χ^2_1 [Mantel Cox] = 0·99, p = 0·32) between cases positive and those negative for HPV 16 DNA. There was no evidence to indicate that HPV 16 DNA copy number or integration influenced response rate, duration of response, or survival, although this observation was based on data from small subgroups of HPV 16 DNA positive cases.

Age-distribution of HPV 16 DNA Positive Subjects

Tumours arising in cases aged under 40 years of age were less frequently associated with HPV 16 DNA than were those arising in women aged 40 years or over (χ^2_1 = 4·74, p = < 0·05). However, there was no significant difference between the overall age-distributions of cases with HPV 16 positive and those with HPV negative tumours (Mann Whitney U = 198·0, p = 0·261). HPV 16 positive controls were older than HPV 16 negative controls (Mann Whitney U = 30·5, p = 0·013). One of 15 controls under the age of 40 and 8 of 11 controls over the age of 40 were HPV 16 positive (χ^2_1 [Yates] = 9·49, p < 0·01).

To investigate the relation between age and HPV 16 DNA positivity further, 9 variables (age, HPV 16 DNA status, use of oral contraceptives, parity, age at first coitus, age at marriage, number of sexual partners, race, and smoking history) were used in a discriminant function analysis[31] to identify independent factors which could discriminate between 45 cases and 25 controls (2 cases and 1 control with incomplete sexual history data were excluded from this analysis). Before any variable was entered into the discriminant function the F-to-enter was calculated for each variable. At this stage (step 0), the F-to-enter for a variable

TABLE III—COMPARISON OF HPV 16 POSITIVE WITH NEGATIVE CASES

—	HPV 16 DNA positive (n = 31)	HPV 16 DNA negative (n = 16)	Test of equality of the groups	
	..	..	U	p
Continuous variables				
Median age (yr)	51	44	198·0	0·261
Median tumour diameter (cm)	6	4	224·5	0·595
Median parity	2	2	280·0	0·456
Median duration of symptoms (months)	3	3	176·0	0·665
Median brachytherapy dose (Gy)	40·0	45·0	253·5	0·252
Median teletherapy dose (Gy)	35·0	37·5	92·5	0·587
—	..	..	χ^2 (df)	p
Discrete variables				
Age less than 40 years	6 *(19%)*	8 *(50%)*	4·74 (1)	<0·05
Marital history				
Married before 20 years	12 *(39%)*	6 *(37%)*	0·01 (1)	0·93
Ever married	23 *(70%)*	10 *(62%)*	0·69 (1)	0·40
Coital history (29 cases)				
Onset before 17 years	12 *(41%)*	7 *(44%)*	0·02 (1)	0·88
Onset before 20 years	21 *(72%)*	12 *(75%)*	0·03 (1)	0·85
More than 1 sexual partner	24 *(77%)*	10 *(62%)*	4·43 (1)	0·28
Ever smoked	15 *(48%)*	6 *(38%)*	0·51 (1)	0·48
Stage				
IB	8 *(26%)*	7 *(44%)*		
IIA-IIIA	13 *(42%)*	6 *(38%)*		
IIIB	10 *(32%)*	3 *(18%)*	1·81 (2)	0·40
Histology				
Large cell scc (± keratinisation)	23 *(74%)*	13 *(81%)*		
Small cell scc	4 *(13%)*	2 *(13%)*		
Adeno/adenosquamous	4 *(13%)*	1 *(06%)*	0·51 (2)	0·77

scc = squamous cell carcinoma.

corresponds to the F statistic computed from a one-way analysis of variance of the variable for cases and controls. The variable with the highest F-to-enter therefore represents the most significant independent factor for classifying subjects as cases or controls. The two variables with the highest F-to-enter at step 0 were age (F-to-enter [df 1, 68] = 13·07) and HPV 16 DNA status (F-to-enter [df 1, 68] = 5·50). At step 1, age was entered into the classification function as the most significant independent discriminating factor. At the end of step 1, the F-to-enter for HPV 16 DNA status had fallen to 1·84, and neither this nor any of the remaining variables could significantly improve discrimination between cases and controls; by controlling for age-distribution, the apparent difference between cases and controls in terms of frequency of HPV 16 DNA positivity had disappeared.

Discussion

This study shows a 66% (95% confidence interval = 52–80%) frequency of association between HPV 16 homologous DNA sequences and histologically assessed invasive cervical cancer biopsies from 47 women living in the West Midlands, UK. Since no other HPV genotypes were isolated, these data suggest that HPV 16 is the predominant genotype occurring in cervical carcinomas in this region. Previous studies have reported the isolation of HPV 16 DNA from between 17%[32] and 61%[18] of cervical cancer biopsies, and some authors have suggested that these data show geographic variability. However, most have reported HPV 16 data from fewer than 25 patients with invasive cervical cancer.

Estimates of HPV 16 gc/hg in nucleic acids extracted from cervical cancer biopsy specimens showed wide variations both between tumours and within adjacent areas of the same tumour. This observation has been made by others[33] and is supported by in-situ hybridisation studies, which have shown a heterogeneous distribution of viral DNA in HPV-associated cervical squamous-cell carcinoma.[34] Results from in-situ hybridisation studies using HPV 16 RNA probes on tissue sections taken from the biopsy specimens used in this study indicate that, even in tumour with high HPV 16 DNA copy number on Southern blot analysis, only a proportion of cells show HPV 16 associated signal. In view of this, and the variable pattern of cervical cancer tissue morphology, we believe that estimates of HPV DNA copy number per host cell are unreliable in the estimation of individual cervical cancer cell HPV 16 DNA levels. Nevertheless, reconstructions remain a useful indicator of hybridisation sensitivity.

Restriction enzyme analysis suggested that HPV 16 DNA was episomal in 24 of 31 positive cancers. 13 cancers containing episomal HPV 16 DNA were studied further, and in all, the viral genome occurred as concatemeric molecules. In 10, *Hin*dIII cleavage produced a single high molecular weight band with the corresponding *Bam*HI cleavage producing a linear HPV 16 molecule (fig 2). It is unlikely that this *Hin*dIII pattern was the result of integration since no putative junctional fragments were detected in the corresponding *Bam*HI digests. The same *Bam*HI cleavage pattern was observed with the other 3 cases studied further, but in these, the *Hin*dIII cleavage pattern consisted of bands in the 23·6 kb and 7·9 kb (linear HPV 16 DNA size) regions (fig 2). The additional *Hin*dIII band in these cases may be the result of one of three events; (1) disruption of HPV oligomers during repeated phenol/chloroform extractions,[3] (2) the presence of variant HPV-16 DNA molecules which have gained a *Hin*dIII restriction site, or (3) the presence of rearranged HPV-16 DNA molecules in these carcinomas. Further studies are underway to distinguish between these possibilities.

Evidence of HPV 16 DNA integration into host chromosomes was found in 7 of 31 positive cervical cancers (23%, with 95% confidence interval = 8–38%). DNA from two carcinomas gave *Bam*HI or *Hin*dIII patterns which suggested HPV 16 DNA integration at single host genome sites. In one further carcinoma, HPV 16 DNA appeared to be integrated at multiple host genome sites. There was no evidence of HPV 16 integration into host cell chromosomes in control biopsy specimens, but further samples should be analysed before specific conclusions may be made regarding the biological significance of integration.

There was no preferential association of HPV 16 with any tumour type or grade. Biopsies from 2 of 3 well-differentiated adenocarcinomas contained HPV 16 DNA. Although this has been reported before,[32,35] the role of HPV 16 DNA in adenocarcinoma has not been discussed. In view of the known squamous epitheliotropic nature of human papillomavinises, we are unable to explain this finding. Preliminary data (median follow up 20·5 months in cases) suggest that the presence of HPV 16 DNA in carcinomas does not influence the clinical outcome of cervical cancer, but further follow-up is required to confirm these observations. The presence of HPV 16 DNA did not correlate with subjects' marital or sexual history, parity, use of the combined oral contraceptive pill, or smoking habits in

cases or controls. Further studies are needed to investigate relations between HPV 16 and other suspected or known risk factors for cervical cancer.

We have previously presented preliminary data relating to the finding of HPV 16 DNA in full-thickness biopsy specimens from normal human ectocervix.[26] Since HPV are known to have a long latency period, during which they reside as non-replicating DNA in the basal and suprabasal layers of squamous epithelia,[3] it seems likely that the analysis of full-thickness biopsy specimens is a more sensitive method of detecting HPV 16 DNA in normal tissues than is analysis of cervical smear or swab material. Even then, however, the blind sampling method used is likely to cause an underestimation rather than overestimation of the prevalence of HPV 16 DNA in normal cervical tissue since HPV 16 DNA may be unevenly distributed within the normal cervix, as in cervical cancers. These control data suggest that clinical intervention may not be needed in all HPV 16 DNA positive subjects.

In view of recent speculation regarding the role of HPV in cervical neoplasia in young women[25,27,28] we were prompted to examine in detail the relation between age and the presence of HPV 16 DNA in cases and controls. Both groups showed an increasing frequency of HPV 16 positivity with increasing age. There was no statistically significant difference between cases and controls under 40 years of age in terms of frequency of HPV 16 DNA positivity (although this observation was based on data from only 14 cases and 13 controls).

Stepwise discriminant analysis identified increasing age as the single most significant independent variable for discriminating between cases and controls; having controlled for age, whether the subject was HPV 16 DNA positive or not was no longer a significant discriminating factor. This observation indicates that the chance of a subject being HPV 16 DNA positive increased with age irrespective of whether a patient had cervical cancer or not. The data therefore suggest an alternative explanation for the observation that the frequency of finding HPV 16 DNA is lowest in groups of patients with cervical intraepithelial neoplasia grade I, rises in groups of patients with CIN I and III, and is highest in groups of patients with clinically invasive cervical cancer.[16] Since the mean ages of patients with CIN I, CIN III, and clinically invasive cervical cancer are around 33, 43, and 52 years, respectively,[36] the apparent rise in frequency of HPV 16 DNA positivity with severity of disease may be the effect of increasing age. We suggest that future reports of the association of HPV DNA and cervical neoplasia should include details relating to the ages of patients under study and that further epidemiological, clinical, and molecular studies are required to clarify the role of HPV 16 in the aetiology and natural history of cervical neoplasia.

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**Riis et al[1] did indeed demonstrate an effect of calcium supplementation on bone in the forearm midshaft region but there was still a significant loss of bone. Unlike the distal forearm and the spine, where no effect of calcium was observed, the mid-forearm is not a site much prone to osteoporotic fracture.

Recker et al[2] demonstrated a reduction in the rate of change of metacarpal cortical thickness with a large calcium supplement, although there was no significant effect on forearm bone density. Nordin et al[3] found no significant effect of calcium on change in metacarpal cortical area. Ettinger et al[8] were also unable to demonstrate any effect of calcium supplementation alone on metacarpal cortical thickness, forearm bone density, or spinal bone density.

The fact remains that studies of calcium supplementation and fracture incidence are inconclusive, while many years of research have uncovered no convincing effect of calcium supplementation alone in preventing postmenopausal bone loss.

There is little cause for concern in women abandoning calcium supplementation; there is great cause for concern in women believing that calcium supplementation is an effective alternative to hormone replacement therapy.—ED. L.

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INCIDENCE OF COLONIC LESIONS IN STREPTOCOCCUS BOVIS AND ENTEROCOCCAL ENDOCARDITIS

SIR,—Dr Hønberg and Dr Gutschik (Jan 17, p 163) confirm the high incidence of gastrointestinal neoplasms (17%) in patients with *Streptococcus bovis* bacteraemia, as reported by Klein et al.[1] The frequency of colonic lesions, neoplasms, or polyps in patients with *Strep bovis* bacteraemia has varied between 17 and 73%.[2,3] However, no data are available for comparison from a normal population or patients with endocarditis due to other intestinal microorganisms.

We have reviewed 77 infections with group D streptococcal endocarditis in 75 patients who were treated between 1974 and 1984. The incidence of colonic lesions was compared in 34 *Strep bovis* (44%) and 43 enterococcal cases (56%). The mean age and sex of the patients was not different in the two groups. Colonic investigations were done in 46 cases, 23 in each group, at the time of endocarditis. There was no significant difference in the number of barium enemas (total 39), rectosigmoidoscopies (19), or colonoscopies (13) in both groups. There was a higher frequency of diverticula in *Strep bovis* cases, but the difference compared with enterococcal cases was not significant (table). However, polyps were significantly more frequent in the *Strep bovis* group. If we consider the 32 patients who had endoscopic evaluation of the colon, a polyp or neoplasm was detected in 12/18 (67%) *Strep bovis* cases, which was significantly different from the frequency (3/14, 21%) in the enterococcal group ($p < 0.02$). An intraepithelial carcinoma was detected in 3/12 *Strep bovis* cases with polyps but not in the enterococcal cases.

Furthermore, a colonic carcinoma had occurred ten years before *Strep bovis* endocarditis in 1 case. 3 patients had a colonic carcinoma diagnosed more than 1 year after endocarditis, 2 in the *Strep bovis* group and 1 in the enterococcal group. Overall the frequency of colonic carcinoma was significantly higher ($p < 0.05$) in patients with *Strep bovis* endocarditis, 6/34 (18%) than in patients with enterococcal endocarditis, 1/43 (2%).

COLONIC LESIONS IN PATIENTS WITH GROUP D STREPTOCOCCAL ENDOCARDITIS WHO HAD COLONIC INVESTIGATIONS

Lesion	Enterococcal endocarditis (n = 23)	*Strep bovis* endocarditis (n = 23)	Comparison between groups
Diverticula	5	10	NS
Polyps	3	12	$p < 0.01$
Total	8	17*	

*Both lesions in 5 cases.
NS = not significant.

Our study confirms the higher incidence of colonic polyps and neoplasms in patients with *Strep bovis* endocarditis compared with enterococcal endocarditis and emphasises the need for systematic colonoscopy to investigate possible colonic carcinoma in these patients. The data accord with the increased faecal carriage of *Strep bovis* in patients with premalignant polyps and neoplasms.[4]

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MANAGEMENT OF MILDLY ABNORMAL CERVICAL SMEARS

SIR,—There is considerable debate about the role of colposcopy in the management of mildly abnormal cervical smears. Mild dyskaryosis progressed to cervical intraepithelial neoplasia stage 3 (CIN 3) within two years in about 25% of cases[1] and there is evidence that a significant proportion of women with cytologically mild atypia have more severe underlying disease.[2,3] In our own clinic CIN 3 was diagnosed histologically in 25%, and CIN 1 or 2 in 50%, of women whose smears showed only borderline dyskaryosis. These findings and the high false-negative rate of cytology in the detection of CIN[4,5] have led to the call for immediate colposcopy of women with mildly abnormal smears. Little is known about the views and current practice of those pathologists who are routinely responsible for reporting on smears.

We have surveyed current management of mildly abnormal smears by 18 consultant histopathologists and cytopathologists from different districts in England and Wales, who attended a recent colposcopic pathology course at our hospital. The numbers of cervical smears screened in these laboratories range from 8000 to 30 000 annually. Only 5 pathologists referred women with mild atypia immediately to gynaecologists, including 3 referrals to colposcopists (table). Repeat cytology is currently used by almost three-quarters of pathologists in the management of mild dyskaryosis, and by all the pathologists in the management of borderline dyskaryosis and inflammatory atypia, although a few recommend colposcopy if a repeat smear shows the same abnormality. The wide range of variation between pathologists in the frequency of repeating the smear reflects uncertainty among pathologists about the use of cytological follow-up for these women. 11 of 13 pathologists practising repeat cytology wanted to refer their patients to colposcopists if facilities were available.

Our findings indicate that most women with mildly abnormal smears in England and Wales today still have no access to

CURRENT MANAGEMENT OF SMEARS SHOWING MILD ABNORMALITY

Management	Original cytology result		
	Dyskaryosis		Inflammatory atypia (n = 16)
	Mild (n = 18)	Borderline (n = 18)	
Cytology follow-up (mo):			
0	1	2	5
3	3	6	6
6	9	9	5
12	0	1	0
Immediate colposcopy	3	0	0
Colposcopy if abnormality persists on cytology	(3)	(7)	(4)
Gynaecological referral	2	0	0

colposcopic examination, although most consultants responsible for the district cytology services are convinced that there is at least a prima facie case for immediate colposcopy as the best management for such cases. Several pathologists also expressed serious concern at the ethical and potential medicolegal problems of continuing to offer to women treatment that the doctor believes to be less than satisfactory. Our survey underlines the call for more resources for colposcopy and the pathology services needed to support it. Our survey also shows that this is a nationwide problem. There is a need for a coordinated national effort to determine the true place of colposcopy in the management of the abnormal smear, and to investigate and debate openly the cost-benefit of the alternative approaches before more potentially avoidable deaths lead to an outcry against individual consultants and a public demand to know why the health service and the medical profession have failed to act.

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COLPOSCOPY

SIR,—Your editorial (Feb 28) argues for an expansion of colposcopy on the grounds that cervical screening is an unreliable method of detecting invasive squamous carcinoma of the cervix. The argument reflects a lack of understanding of the purpose of cervical screening and the concepts underlying the national campaign for the prevention of cervical cancer. Cervical screening is not intended for the diagnosis of invasive lesions; its aim in the UK is to detect preinvasive lesions to prevent the development of invasive cancer.

Although cytology has a false-negative rate of 7–17%[1] and preinvasive lesions may be missed, errors of diagnosis are compensated for by regular repeat screening. Proof of this is provided by the success of screening programmes in Aberdeen, British Columbia, and elsewhere, where comprehensive screening has achieved a remarkable decline in clinical cancers. In addition, Parkin[2] used computer simulation to show that 77% of invasive cancers can be prevented by three-yearly screening between the ages of 20 and 64, assuming an 80% uptake by women at risk and a test sensitivity of 70%. We are screening for cancers with a long preinvasive stage (still the large majority of cancers), and the failure to detect CIN on the first screen does not negate the value of the programme.

You fail to emphasise another very important point. It is most unwise to use cytology for the primary diagnosis of invasive cancer since smears from these lesions often contain blood and pus which obscures the epithelial cells, making a reliable cytological diagnosis impossible. The primary diagnosis of invasive cancer is a clinical one depending on a careful examination and history by the clinician taking the smear; and a clinical suspicion of malignancy must always override a negative cytology report. The missed invasive cancers complained of in your editorial could possibly reflect a failure of clinical judgment.

You propose colposcopy for all minor degrees of cervical atypia and low grade CIN. No national records are available to indicate how many women would require this service but we identify 10 such cases for every case of CIN 3. About 20 000 cases of CIN 3 are diagnosed in the UK every year so we may expect 200 000 more women to require colposcopy. Since there are only 4000 new cases of invasive cervical cancer each year, the risk of progression must be very low and 196 000 women will be referred for colposcopy and biopsy unnecessarily. Can this approach really be justified when a well-planned cytology programme can achieve equally good results?

Surely, what is needed is a sound screening strategy which will prevent most cancers, an effective call-and-recall system, and a colposcopy service for women most at risk. Colposcopy should be available for those women with a cytological diagnosis of CIN 3, a clinical suspicion of invasive cancer, or repeated unsatisfactory smears that do not permit reliable cytological diagnosis.

The colposcopy resources available are already under strain. If we adopt the policies you recommend, anxious women with inflammatory smears will be referred to colposcopy clinics while women at much greater risk will be pushed further down the queue.

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SIR,—Your editorial review of the evolution and management of CIN fails to discuss the full impact of colposcopy in modern clinical practice. The increase in precancerous and cancerous lesions of the cervix has been matched lately by a similar rise in the incidence of human papillomavirus (HPV) infection of the lower genital tract. The association of HPV infection with premalignant and malignant lesions of the cervix is well established.[1,2] Most cervical HPV infections are subclinical, requiring colposcopic evaluation[3] for diagnosis, treatment, and follow-up. Successful therapy can only be achieved by preventing reinfection by an infected sexual partner. Penile HPV infection does not always present as frank condylomas and subclinical infection may also require the equivalent of colposcopic assessment before treatment. Many departments of genitourinary medicine, where most genital HPV infections are treated, run regular colposcopy clinics.[4] Such departments successfully manage cervical HPV lesions and associated minor dysplasias without recourse to their colleagues in gynaecology. The colposcope can also be of value in the assessment of anorectal warts.

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CIPROFLOXACIN RESISTANCE

SIR,—Dr Hodson and colleagues (Jan 31, p 235) rather dismiss the development of *Pseudomonas* resistance to ciprofloxacin. However, it would have been informative if they had included data on median minimum inhibitory concentrations (MIC_{50}) at the beginning and end of treatment.

We are concerned about the development of such resistance in

In reply: My recent article[1] has generated a great deal of national media publicity. Two issues have been raised with exceptional frequency and I would like to address each of these briefly.

First, it has been suggested that if an adopted infant has been found subsequently to have a serious mental or physical disability, the natural mother should be "protected" from this information. I do not accept this argument. Many natural mothers' fantasies about their children's fate are far worse than even this kind of reality. In addition, such children have usually received a great deal of love and caring together with the best possible professional help — further vindicating the natural mother's decision to relinquish. The emergence of such conditions often carry genetic implications of which, I believe, the natural mother should be made aware.

Secondly, while relinquishment in the 1980s clearly occurs under very different and more humane circumstances than those experienced by most of the women in my report in the 1960s, I do not think that the possibility that adverse psychological sequelae might have occurred because of relinquishment is thereby rendered a "dead issue". To highlight but one aspect, the option of keeping the child in the 1980s is a very real one for many of these women in view of the support systems that are available and the much reduced stigma of illegitimacy, unwed pregnancy and single motherhood. It remains to be seen whether, in the year 2000, when the present generation of women look back 15–20 years upon their decision to relinquish, they will experience more or less guilt than those who saw themselves as having no viable option in the 1960s other than relinquishment. I would speculate that their burden of guilt may well be heavier rather than lighter since their relinquishment is now very much more "by choice".

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Human papilloma virus and cervical cancer

To the Editor: I read Suzanne Abraham's letter (MJA, February 3, 1986) expressing worries about the need for accurate information to be transmitted to the population by health professionals in relation to the papilloma virus and cervical cancer, and some of the resultant press publicity, with interest.

I think she is expecting a bit much of young people who were asked to answer questions at a shopping centre. Scientists are still somewhat uncertain about the papilloma virus and complex questions related to the control of cervical cancer remain unanswered.

Some questions trouble me. Even if papilloma virus is the probable major cause of cervical cancer, is it the only one? What was the cause of cervical cancer in the 1930s, 1940s and 1950s? The incidence of the disease was declining before the introduction of the Papanicolaou smear in many parts of the world (including Australia). Sexual freedom arrived later.

Furthermore, the major group at risk of cervical cancer at present is unscreened women of over 40 years of age (approximately 250 000 women of an at-risk total of 1.4 million in Victoria). Cervical cancer occurs most commonly in this population which is a difficult group to encourage to be screened. Are we likely to attract such women into being screened for cervical cancer by telling them that cervical cancer is a sexually transmitted disease? I have been concerned for some years over the dogmatic way in which this disease was classified by some as a disease of "promiscuous women". Research then discovered that "promiscuity" could be characteristic of the male partner, not the female partner, and that some papilloma virus strains are prime candidates as causes.

What is the best way to handle the problem? First of all, we should not become hysterical, as we did with AIDS. Cervical cancer is eminently controllable by the intelligent use of the Papanicolaou smear test. It may also be substantially preventable by means of improved public knowledge and sensible barrier contraceptive practices.

We need to achieve better agreement among scientists as to who should be screened and when, by whom, and who should pay for this. We will learn a good deal about the biology of the disease by screening younger persons over time, but we will not save many lives. We will save a significant number of lives by screening women aged over 40 years, at a lower cost. Whether this population is advised to undergo screening every six, 12, 24 or 36 months is much less important than whether we succeed in screening all of them once. Therefore, we require some well researched public education programmes that are aimed at achieving a first-ever screening of the at-risk population that we have so far failed to reach (this is planned for this year in Victoria).

Informing young people is going to be important but the message is fairly complex. Fortunately, it doesn't differ substantially from the one that specialists in sexually transmitted diseases would wish to transmit about herpes simplex and the other sexually transmitted diseases.

We certainly require further research into the infectivity of the papilloma wart virus, for example, is it transmitted as a routine to every sexual contact or are individuals infective transiently or intermittently? If so, for how long? It is difficult to counsel people without this information.

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Dangerous dunnies and avoidable accidents

To the Editor: Although the red-back spider that lurks underneath the outhouse seat now seldom threatens the regularity of Australians, the toilet is not without its risks. I wish to report two cases which illustrate that the toilet still poses a significant threat to young infants.

The first, a very lively and active 13-month-old male infant, was found by his mother with his head over the toilet bowl and trapped by the toilet seat by the neck across the rim of the bowl. He was cyanosed and unresponsive, but still breathing. He was rushed to hospital by ambulance. Examination showed him to be a large boy whose weight of 12.7 kg was above the 90th percentile for age. He was crying irritably. He had multiple petechiae about his head and neck, a bruise on his right temple and erythematous marks about his neck and across his shoulders. He was hyperreflexic. His clinical features were considered consistent with asphyxia. He was treated with phenobarbitone and dexamethasone and made a full recovery.

The second — a 14-month-old boy — was found hanging over the toilet bowl, again, trapped at the neck by the toilet seat. He was wearing a one-piece sleep suit with cloth feet. He was blue and unresponsive but improved spontaneously after removal from his entrapment. When seen in the Emergency Department he had a frontal haematoma but no other signs of injury and was allowed to go home. Subsequent review showed him to have suffered no ill-effects.

Childhood injuries are no accident. Recognition of the roles of the host, the agent and the environment in childhood injuries makes many such events predictable and preventable.[1] It is perhaps surprising that more children are not asphyxiated as these two boys were. The predilection for boys to damage themselves more commonly than do girls becomes apparent in the first year of life and is exaggerated thereafter.[2] This difference may in part reflect differences in temperament which manifest very early in life and have been shown to be related significantly to proneness to accidents.[3]

Accidents in childhood reflect the developmental stage.[4] Early in the second year of life infants are inquisitive but do not have the cognitive ability to recognize danger or to remember warnings. They are mobile but are often still unsteady and without recovery skills. The relative size of their head in relation to trunk and legs makes them more likely to topple over. In the second case, the child's clothing probably impaired his grip

upon the floor and rendered him even more vulnerable. The agent in these accidents, the toilet bowl, was accessible and of the right height to pose a threat to young infants, but would not do so to older or younger children. The single most important contributing factor to these injuries was the lack of supervision of the children. Failure of supervision may only be transient, but is critical in allowing a child access to danger.

These patients have presented after unusual accidents, but are a forceful reminder of the dangers that abound in the home. Recognition of the different factors that produce childhood accidents will enable many of them to be prevented. The porcelain bowl — often a source of comfort — nearly resulted in disaster for these toddlers.

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Ranitidine and hypertension

To the Editor: Ranitidine, a H_2-receptor antagonist, is considered to be very effective in the therapeutic management of peptic ulcer disease. The drug appears to be safe and only minor side-effects have been reported.[1]

Recent observations have described an hypertensive action of ranitidine;[2] this side-effect may be relevant clinically.

In our department the arterial blood pressure of 69 subjects (41 men: mean age, 44.7 years; range, 30–70 years; 28 women: mean age, 32.6 years; range, 21–81 years), with an endoscopic and histological diagnosis of peptic ulcer disease, was measured twice a day for 10 days before ranitidine treatment was commenced, and at weekly intervals for at least six months during treatment.

The blood pressure was measured by means of a mercury sphygmomanometer; the diastolic blood pressure was taken to be at the disappearance of the Korotkoff sounds (phase V). Normotensive subjects did not receive any other drugs; the 10 subjects with pre-existing hypertensive disease continued their antihypertensive therapy. All patients received 150 mg of ranitidine twice a day by mouth and were instructed to eat a normal diet without sodium restriction.

After 16 months of ranitidine treatment, one normotensive patient (a man aged 54 years) developed an increase in blood pressure levels — mean of weekly measurements over two months, 165.5/95.2 mmHg compared with 126.4/80.7 mmHg, the mean of the values measured weekly over the preceding 16 months. Lowering of the ranitidine dosage to 150 mg a day at bedtime and dietary reduction of the sodium intake reduced the recorded blood pressure values to within the normal range over two weeks.

The other 58 normotensive patients did not show any changes in mean blood pressure levels (121.5/82.3 mmHg before as compared with 119.7/79.8 mmHg after ranitidine therapy). All 10 patients with pre-existing hypertension did not show significant variations in mean blood pressure values after six months of treatment with ranitidine (155.2/98.4 mmHg compared with 154.7/96.8 mmHg).

This observation indicates that ranitidine may indeed cause hypertension as a side-effect but that its occurrence is infrequent and may represent an idiosyncratic response. Nevertheless, this potential effect has to be considered when an increase in arterial blood pressure is found during treatment with ranitidine.

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Side-effects of corticosteroid agents

To the Editor: In the excellent article on the side-effects of corticosteroid agents[1] only brief mention was made of myopathy. An unusual form of myopathy, of which I have seen an extreme example, is weakness and consequent divarication of the recti abdominis muscles which leads to a huge ventral hernia.

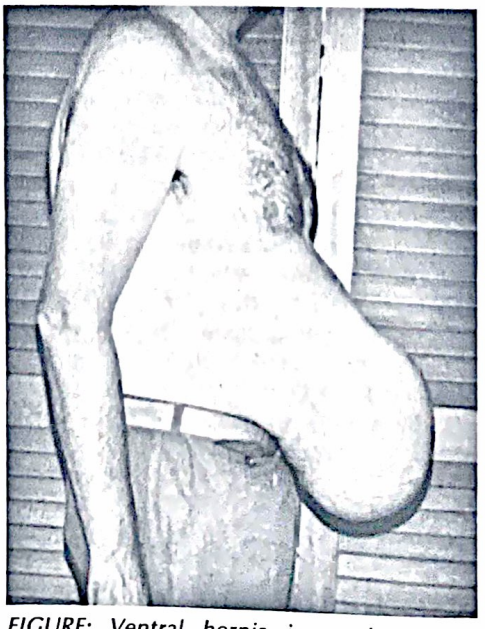

FIGURE: Ventral hernia in corticosteroid-induced myopathy.

My patient is a 44-year-old man with the unhappy combination of bilateral lower lobe bronchiectasis and severe corticosteroid-dependent asthma. He has been taking prednisolone since a near-fatal episode of status asthmaticus in 1966 and it has not been possible to reduce his dose below 15 mg a day. In 1974 he developed a ventral hernia which enlarged rapidly. Two senior surgeons have rejected him for operation and the hernia has become progressively worse (Figure). It is supported by a harness and so far the skin, which is the only covering of the intestines, has remained healthy though greatly stretched. He also has some wasting of the gluteal muscles.

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Malarial prophylaxis

The publication *Malaria prophylaxis for Australians travelling or temporarily resident overseas*[1] (which has been sent to all registered medical practitioners) was prepared by a working party that included Dr Antonia Bagshawe and which considered *all* the current scientific data in this area, including unpublished work. Consequently one wonders how Dr Bagshawe can comment that "recommendations for protection against drug-resistant strains of *P. falciparum* (which is becoming increasingly difficult) do not conform with generally accepted practice" (MJA, March 17, 1986).

The prescription of chemoprophylaxis for travellers to and residents of countries with chloroquine-resistant *Plasmodium falciparum* malaria is a most difficult task for medical practitioners. In our publication the risk situations for the acquisition of malaria, including chloroquine-resistant *P. falciparum* malaria, are spelt out. However, this information is followed later by what has been called a "blanket" recommendation for the use of chloroquine and dapsone/pyrimethamine (Maloprim) in all situations in countries from which chloroquine-resistant *P. falciparum* malaria has been reported.

It was our expectation that medical practitioners would make a risk assessment for individual patients and prescribe accordingly. Thus, for example, in Thailand, a country with chloroquine-resistant *P. falciparum* malaria, *no* malarial prophylaxis would be prescribed for a tourist who was staying in