

SCAN

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B A C

British Association
for Cytopathology

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Editorial

Sharon Roberts-Gant

Autumn is upon us which means it's time for this year's second edition of SCAN. The BAC has been in existence for three years now which means that we will soon see changes in the Executive Office bearers and as such this will be the last time that Karin Denton writes for us as President of BAC and Allan Wilson as Chairman. However Allan will be contributing to the next edition as by then he will have taken the reins as President. There has been several changes within the Executive team, you may meet the new members on page 17.

The BAC Executive have been busy and Louise Smart has provided us with both a membership update and an update from the Code of Practice working group whilst Alison feeds back on the well-received BAC tutorial held in July as well as bringing us some exciting news about the 2016 BAC conference (but you will have to read SCAN to find out what it is!). We also have some feedback on the IFCPC 15th World Congress, which was held in London earlier this year from Kay Ellis, and she has shared an interesting experience in Ethiopia with us.

Jesper Bonde discusses cervical screening in Denmark, its historical background and the forthcoming challenges, the article is a follow up from his presentation on 'The Horizon Study' at the BAC 2013 Scientific meeting. To further exercise the 'little grey cells' Drs Williamson and Hemming have provided three case studies for you to deliberate over whilst Marilyn Bletchley has sent in a conventional cytology quiz to tease the memory of the LBC readership and challenge those still involved with the conventional technique. There is a bit of fun entitled Cyto(ani)morphology on page 19!

I hope you enjoy this issue of SCAN and I'd like to thank the contributors for their support.

Sharon

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Editor Andrew Evered.



INFORMATION FOR CONTRIBUTORS

Articles for inclusion in SCAN can be emailed to the editor if less than 1MB in size or supplied on CD/DVD or memory stick. Text should be in a standard text format such as a Word document or Rich Text Format (rtf file). Please supply images as separate files in tiff or high quality jpeg files at a resolution of not less than 300 dpi (600 dpi if the image includes text). 35mm slides and other hard copy can be supplied for scanning if no electronic version is available. Graphs are acceptable in Excel format.

If you are unable to supply files in the above formats or would like advice on preparing your files, please contact Robin Roberts-Gant on 01865 222746 or email: robin.roberts-gant@ndcls.ox.ac.uk



President's Column

Karin Denton

This will be my last column as BAC President, before I conclude my term of office in the autumn. It has been a very great honour to be the inaugural president of a new professional association, and a pretty unique one at that. Forming the BAC has been a great achievement and I am sure in years to come it will be seen as having been a trail blazer and a role model for strengthening professional bodies by working together.

One of the great pleasures of being part of the BAC is working with extremely dedicated and expert people, and I particularly want to take this opportunity to thank Amanda Herbert for all her work as editor of *Cytopathology*. The journal is one of the great assets of our association and continues to go from strength to strength. It is also a great pleasure to welcome the incoming editor, Professor Mina Desai who will take over in 2015.

While I leave the BAC in good health and in good hands, these are still challenging times in cytology. The major waves of reconfiguration of cervical cytology services are now mostly complete, but the last few years have been stressful for our members. The new technologies coming in are exciting but more change is on the horizon. However when I was at a cytology meeting elsewhere in the world I was asked why the BAC was not opposing HPV testing if it put members jobs at risk. It is a reflection of our

professionalism and patient centred approach that I have never once heard any BAC member ask this. I really do feel we as an association put women being screened at the heart of everything we do.

In diagnostic cytology things also remain difficult. There is still a lot to do to raise the profile of cytology amongst histopathologists and clinicians, to make sure that British patients reap the benefits of diagnostic cytology which are routinely available in Europe and North America. The BAC has moved to the forefront of this campaign, but it is other bodies which need to make the changes which will make a difference. This is doubtless one of the areas which the new President and executive will progress.

Something which will help raise our profile would be the hosting of an international meeting – watch this space, more information will follow.

I look forward to seeing you all at our annual meeting, which as usual has excellent scientific content, and also encourage you all to strengthen the BAC by promoting membership to colleagues and by coming forwards with suggestions or volunteering to help organise the activities of the BAC.

It has been an honour and a privilege!

Karin Denton, President BAC

Coming soon...BAC Code of Practice for Cervical Cytology Laboratories

Louise Smart

BAC Executive, Code of Practice working group

It is now four years since the BSCC published its 3rd Code of Practice for Cervical Cytology laboratories (CoP).

This comprehensive document, which can be accessed from the BAC website¹, brought together existing guidance and made recommendations for best practice. The intention was for regular updating of that publication and, as much is changing for cytology laboratories, the BAC feels that now is the time to revise the CoP if it is to continue to be relevant to current practice and changes in technology. We aim to produce a shorter document in a format that remains easy for laboratory staff to access with an emphasis on e-links to relevant guidance endorsed by the BAC, such as NHCSP, IBMS and Royal College of Pathologists' documents. As with the previous BSCC document, the CoP will be published on the BAC website. We hope to update it annually to reflect ongoing developments and new guidance. With the help of the BAC membership, we intend

to continue to develop guidance in the areas where changes are greatest and existing guidance is lacking.

The areas covered by the CoP include staffing roles and responsibilities, workload, sample transport, processing and reporting, quality control and performance monitoring, IT requirements, multidisciplinary team working and education and training. There is also a new section to cover testing for high risk HPV. Important key principles are emphasised and differences between the four UK nations are highlighted.

Members will have the opportunity to comment on a draft of the CoP and we hope to be able to launch this updated Code of Practice at the BAC Annual Scientific Meeting in October 2014.

¹http://www.britishcytology.org.uk/uploads/BSCC_COP_2010.pdf

Chairman's Report

Allan Wilson



Unlikely as it may seem, it has been three years since I became the first Chairman of the BAC. My term has passed in a flash and this will be my last chairman's report for *SCAN*; in October I will become President of our Association. On a personal level, the last three years have been an incredible experience. It has been an extraordinary privilege to lead the BAC and to work with my fellow executive members over the last three years.

There was a tremendous amount of effort by all concerned during the merger process between BSCC and NAC and the first year was mainly about forming the executive into a cohesive committee and confirming roles and responsibilities. The last two years has delivered many important initiatives including the non-gynae NEQAS Technical EQA scheme championed by Paul Cross and the non-gynae Advanced Specialist Diploma launched by Tom Giles last year. However, it has been noticeable over the last 12–18 months how difficult it has been for executive members to find the time to commit to executive actions. Local pressures and staff shortages have lead to increasing pressure on senior staff within their base labs and a resultant loss of time to commit to BAC. This is a statement of fact and should not reflect on the huge amount of work that has been carried out by your executive. Turnover of membership of any executive body is healthy, and is required for all societies to develop and evolve, but when executive members resign due to work pressures a worrying trend has begun.

As you will be well aware, the journal *Cytopathology* is published by Wiley on behalf of the BAC. The journal was launched by the BSCC and has gone from strength to strength as the only *Cytopathology* journal published in Europe. A succession of dedicated editors has ensured the success of our journal and the current editor, Amanda Herbert has edited *Cytopathology* since her appointment in 2007 and will stand down as editor at the end of December 2014. The new editor of *Cytopathology* is, to use a Scottish phrase "a well kent face" (feel free to use Google translator!), Mina Desai who should not require an introduction to many readers of *SCAN*. Mina will assume her new role in January 2015 and is currently working closely with Amanda in a "shadowing" phase and has already started to assess new submissions to the journal. I am certain that Mina will continue the high quality work of previous editors and ensure the continued success of *Cytopathology*.

One of the challenges faced by the executive in the first few years of the BAC was to clarify the links between our publishers, Wiley and the editorial boards (there are two – advisory and management). Links between the BSCC council that established *Cytopathology* were strong but over the years as the council membership changed, the links became weaker and at the time of forming the BAC there was very little knowledge on how the journal "worked" and how the

BAC executive influenced the membership of the editorial boards and content of the journal. It has taken a tremendous amount of investigating and close working with Elizabeth Whelan from Wiley to finally establish the relationship between the journal and the executive and to use another probably more recognised Scottish phrase, bring *Cytopathology* back into the "body of the Kirk". We are now clear on how the journal fits into the BAC and this has been recorded to ensure we continue to strengthen these important links in the future.

One final word about *Cytopathology*. Elizabeth Whelan from Wiley has been pivotal in ensuring the success of *Cytopathology* and without her help and support the journal would not be the success it is today. Elizabeth is changing role within Wiley and will not have such a direct input into our journal in the future. On behalf of the executive, I would like to sincerely thank Elizabeth for all her hard work since *Cytopathology* was launched and wish her every success in her new role.

Still on the theme of changes in personnel, there will be two more changes to our executive, Karin Denton and Fraser Mutch have decided to stand down from the BAC executive and will not seek re-election. Fraser and Karin have been long serving members of both the BSCC Council and BAC executive and have been instrumental in the formation of the BAC and have contributed hugely to the success of the BAC executive. Karin has led from the front in her role as the first President of the BAC and will be a very hard act to follow. On behalf of the executive I would like to thank Karin and Fraser for all their hard work during their membership of the executive. The nomination process for new members of the executive is underway and the outcome will be announced at the Birmingham meeting in October.

Since the last edition of *SCAN*, the executive has agreed to host the 2016 EFCS meeting in Liverpool. This is a tremendous opportunity for us to demonstrate our high standards to our European colleagues and to learn from their experience. Organising a meeting on this scale will be a huge undertaking and work has already started to put the committee structure in place to deliver a successful conference.

Finally, this could be the last report I write for *SCAN* from within the United Kingdom! The outcome of the September referendum is looking like it might be on a knife edge and the success of the Commonwealth Games (at time of writing) may tip some undecided voters into the Yes camp. It will be an interesting few months for the UK as a whole. Whatever the outcome, the BAC will continue to represent cytology across all nations in the British Isles.

Mr Allan Wilson,
Chairman BAC

IFCPC 15th World Congress for Cervical Pathology and Colposcopy

26th –30th May 2014

The Queen Elizabeth II Conference Centre, London, UK

Kay Ellis

The British Society for Colposcopy and Cervical Pathology (BSCCP) hosted the International Federation for Cervical Pathology and Colposcopy (IFCPC) 15th World Congress in London in May 2014. The BSCCP invited Dr Karin Denton, President of the BAC to host a session at this international meeting. This was too good an opportunity for the BAC to miss and gave us a wonderful opportunity to promote our association.

The congress was held at The Queen Elizabeth II Conference Centre in London. The location was amazing next to the Houses of Parliament, Big Ben, London Eye and Westminster Abbey (Figure 1). The conference centre was massive with rooms on different floors and extensive space for the trade exhibition. The rooms boasted British names like the Churchill Room, Nightingale Room and Mountbatten Room to name a few.



Figure 1: The Queen Elizabeth II Conference Centre, London

It was estimated that there were over 1200 delegates attending from all over the world including a few familiar faces from the UK and BAC plus a few of my friends and colleagues from Sheffield. There were over 350 e posters and just under 100 oral submissions — that's impressive. The programme was extensive too with up to five parallel sessions at one time. It was difficult to choose which session to attend and at times I wish I could have split myself in to two or three.

The daily sessions started quite early and my hotel was situated about 30 minutes away. It was a pleasant stroll when the weather was OK but we had mixed weather – typical English weather.



Figure 2 View from lecture theatre

Tuesday

The first session I attended was the American Programme where Dr Alan Waxman and Dr Herschel Lawson outlined the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for cervical screening and their algorithms for managing women with cervical disease. If we thought the English pathways were complicated, you should the American algorithms. In fact they are so complicated that the ASCCP have developed an app to help you work out which patient pathway to take! HPV testing is used as a co-test with cervical cytology i.e. HPV and cytology are both done. There still seems to be some reluctance to use HPV testing only despite one of the HPV platforms gaining FDA approval for primary HPV screening. This session was vastly oversubscribed with delegates crammed in everywhere.

The next session after coffee that I decided to go to was the Indian programme where there were numerous short presentations on aspects of trying to deliver a cervical screening programme in a developing country with a lack of resources. Visual inspection of the cervix using acetic acid (VIA) is quite a common technique used in poor resource settings as it is a test which can be done easily and does not require much equipment. Acetic acid is applied directly to the cervix and left for 30-60 seconds, after which the cervix is visually examined with the naked eye and a lamp. Pre-cancerous lesions turn white when combined with acetic acid and a normal cervix with no precancerous lesions will not change colour. This allows a physician to perform a see and treat procedure there and then.

A mediocre lunch was served in the extensive trade show. This was an opportunity to catch up with some old faces plus meet some new ones.

The main lectures of the afternoon were in the Churchill Auditorium. This series of lectures covered cervical screening strategies from an international perspective covering the use of VIA and the impact of the use of the HPV vaccination. Professor Julietta Patnick, Director of the NHS Cervical Screening Programme (NHSCSP) gave an overview of cervical screening in England. The take home message from Julietta's talk was the success of the programme and that everyone is certainly proud to be part of it.

The day finished off with the drinks reception and more opportunities to go around the trade show. I bumped in to Jesper Bonde who has written a very interesting article for us in SCAN about cervical screening in Denmark.

Wednesday

Today required an early start as the BAC session began at 8.30 am and I was first on the programme. I was pleasantly surprised as there were about 300 delegates there. We even took our BAC banners to put on the stage. I spoke about HPV Primary Screening and it seemed to be well received, I certainly had quite a few people coming up to me in the breaks to ask questions and get further information. Claire Geary gave a very nice presentation with one of her colposcopy colleagues about the importance of the colposcopy multidisciplinary team meeting. It certainly reinforced the importance of these meetings. Dr Paul Cross closed the session with the importance of the invasive audit and the need to review the full history of the women. Some of the delegates were very noisy through the session and I had to tell them to be quiet.



Figure 3 BAC stand at the IFCCP World Congress

I attended the proffered paper session after the break. During the lunch break I caught up with Matejka Rebolj who works with Jesper in Denmark and has spoken for the BAC before. We discussed lots about HPV! After lunch, I attended the session about HPV and the use of molecular markers. The use of molecular markers gets ever more complicated and proliferative — no pun intended! Professor John Tidy

gave an overview of HPV triage and test of cure. There were some really good lectures on HPV markers. John Doorbar's talk about molecular markers was fascinating and it was well illustrated by good animation of how the markers work to identify integrated cervical disease. There were more sessions about HPV and further discussions about developing the strategy for cervical screening.

Thursday

It was another miserable day in London as I made my way in to the conference centre. This morning's sessions were about HPV vaccines and the development of a 9-valent HPV vaccine which should prevent up to 90% of cervical cancers. After the coffee break, there was a debate about 'Where did colposcopy go after the Crossroads' featuring Maggie Cruickshank, Mario Sideri, Henry Kitchener and Jose Jeronimo. The debate included using different methods for identifying disease and the use of different grades of staff. Another speaker spoke about grading cervical disease using the 'Swedescore' system. Colposcopic images of the cervix after VIA can be graded against this system enabling the colposcopist to assess the extent of cervical disease.



Figure 4 Professors John Tidy and Henry Kitchener

Unfortunately I had to leave before the sessions had finished. What was my impression of the congress? It was a massive conference with probably too many parallel sessions to choose from. Although it was a colposcopy and cervical pathology meeting the main focus was on HPV and the new vaccines. It was certainly very interesting and good to meet up with old friends and meet new friends. Hopefully we will have raised the profile of the BAC.

Cervical Cancer Screening in Denmark, Use of HPV technology and the near future

Jesper Bonde,
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Hospital, Hvidovre, Denmark

As a follow up to The Horizon Study presentation at the October 2013 BAC meeting in Manchester, I am writing on the status on the Danish national organised cervical screening programme, our use of HPV technology and some of the challenges in the implementation of HPV technology that will emerge as primary HPV screening moves closer.

The current status of the Danish cervical screening programme was recently reviewed in "Cervical Screening at Cross Roads" (1) by our joint task force between the Department of Pathology, Copenhagen University Hospital Hvidovre, and the Department of Public Health, University of Copenhagen. The review is the basis of this text, though I have expanded and adapted it for this SCAN manuscript. Moreover, both the recently completed Horizon study (evaluation of HPV tests in routine screening) and our on-going Copenhagen Self Sampling initiative have elicited many considerations as to the future organisation of the cervical cancer screening programme in Denmark, which will be discussed here.

Background: Denmark has a high prevalence for cervical cancer; Reason unknown....

In Denmark, a pilot screening programme was started in 1962, and was expanded into a number of county wide programmes in 1967, in parallel with opportunistic screening in other counties from 1969 onwards. All of this was integrated in 1986 into an organised national screening programme implemented by the former counties. In Denmark, all screening recommendations are issued by the Danish Medicines and Health Authority (the former National Board of Health), but the operational responsibility for screening rests with the five regions since their creation in 2007. A considerable amount of time elapsed before the recommendations were implemented nationwide. As the nationwide implementation of the screening programme was completed, the incidence of cervical cancer decreased from 34 per 100,000 in 1966 to 11 in 2000, and stabilized at this level afterwards. Mortality from cervical cancer has gone down steadily from 13 per 100,000 in 1956 to about 2 per 100,000 in the 2000s (2) (Figure 1). The recommendations were updated and

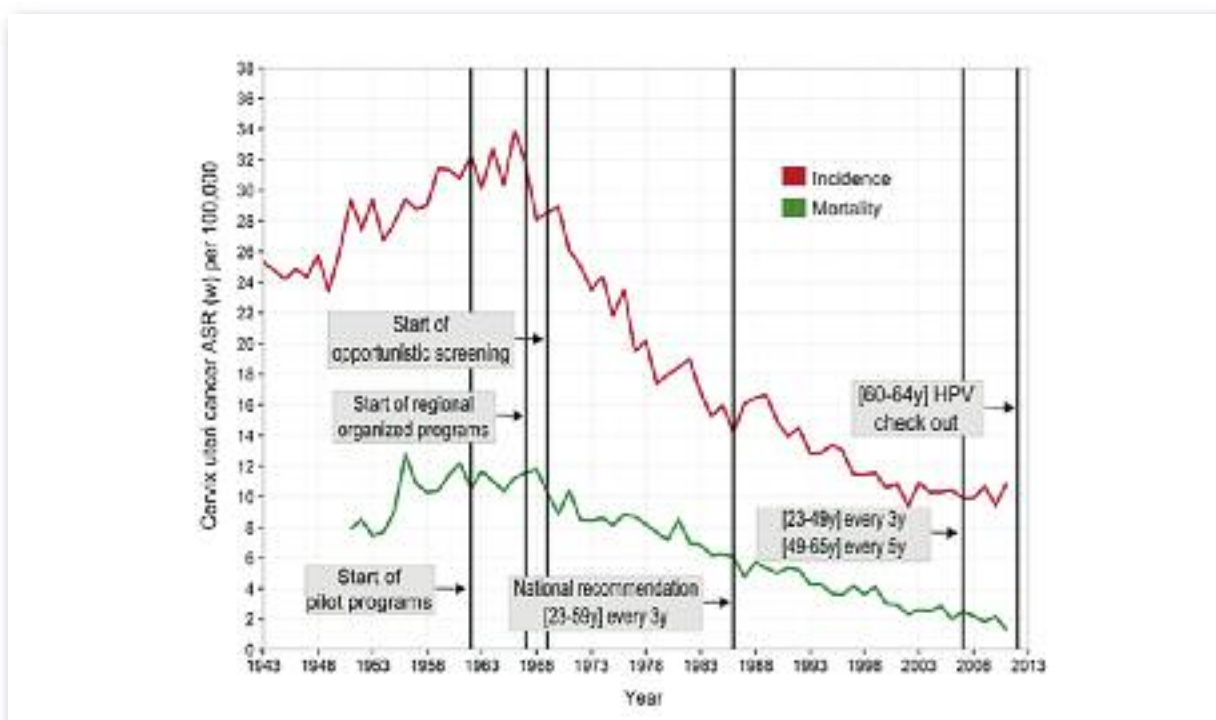


Figure 1. Age-standardized incidence and mortality rates of cervical cancer per 100,000 (World Standard Population) in Denmark 1943–2011. Changes to the cervical screening activity indicated in gray boxes. Reproduced from Lynge et al. APMIS, 2014 (1).

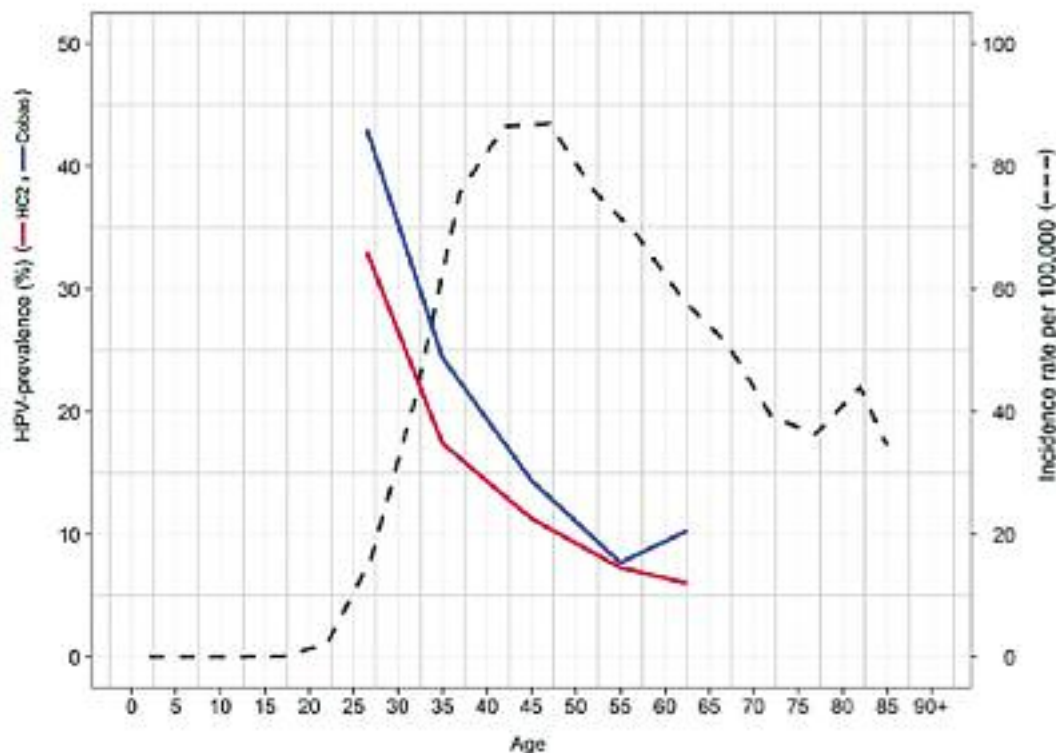


Figure 2. Age-specific incidence rate of cervical cancer per 100,000 in Denmark, 1958–1962 (prior to start of screening), and age-specific prevalence of high-risk human papillomavirus (HPV) per 100 in screened Danish women in 2011. Note that cobas and HC2 were tested on the same samples. Data Sources: NORDCAN and The Horizon Study, (2, 4). Reproduced from Lynge et al. *APMIS*, 2014.

changed in 2007 to recommend screening every third year in women aged 23–49 years, and every fifth year in women aged 50–65 years.

Historical perspective

The pre-screening incidence of cervical cancer in Denmark was from a European perspective rather high, culminating in an age-standardized rate of 34 per 100,000 in 1966 (2). This brings Denmark straight into the international top-10 highest incidence rates for cervical cancer ever recorded (3). Before screening, the incidence rate increased sharply from age 25 to 30 years, and peaked between ages 40 and 45 years. Assuming a 10–20-year latency period of HPV infections, this incidence pattern corresponds well with the present pattern of HPV infections where the prevalence is highest at age 23–29 years (4) (Figure 2). In other words, high HPV prevalence is not a new occurrence: it is reasonable to assume that the HPV infection rate of Danish women has been high for generations.

But why is there this difference in the HPV prevalence between Denmark and the countries we normally compare ourselves to: Sweden, Norway, the UK or the Netherlands?

Obvious explanations could include a relatively early age at sexual debut, a comparably higher average number of sexual partners than several European countries,

especially at young age, etc. Another underlying speculative suggestion could be that HPV infections are strongly dependent on the epigenetic background of the population (host factors); Denmark has a very genetically homogeneous population, in comparison to e.g. the UK where the genetic pool is more diverse. But in fact, little is known on why Denmark differs from our neighbouring countries with respect to HPV prevalence.

The success of the screening programme and its cost

With a reduction in the rate of cervical cancer incidence of 2/3 over 40 years, cervical screening has achieved its purpose. But the programme is also a huge undertaking, establishing itself as one of the largest public health promoting endeavours since WW2. Although the screening coverage is at present only 76% (5), we have 440–460,000 cytology samples per year in the total population of 5.6 million people; 55,000 cervical biopsies; and 7,200 CIN treatments. This has brought down the number of cervical cancer cases from 963 in 1966 to 398 in 2012; and the number of deaths from cervical cancer from 344 in 1966 to 75 in 2011. These numbers indicate that cervical screening is associated with considerable overtreatment as one prevented cervical cancer case comes at the cost of 6–8 CIN treatments (6), and these treatments are associated with discomfort and pre-term birth in later pregnancies (7).

ORGANISATION AND TECHNOLOGY OF THE CERVICAL SCREENING PROGRAMME:

But how do the technology changes affect the performance?

In Denmark, cervical screening is embedded into the medical pathology field and currently carried out in 12 departments across the country. No microbiology departments or private laboratories are mandated to carry out cervical screening, and with the cervical screening being operated by the regional health care authorities this status is unlikely to change. We currently have a national minimum mandatory requirement of 25,000 annual cytology samples to be evaluated per laboratory per year to be active in the screening programme, and this number is likely to increase in the near future to facilitate further consolidation and to improve the quality of the service. In 2012, three of the five regions consolidated the cervical screening programme into fewer departments; our Capital Region was most efficient in this endeavour, by reducing the number of active screening units from three pathology departments into one, now covering in effect 1/3 of the Danish population. The focus towards large scale operations has been an on-going process for many years, and goes hand in hand with implementation of new technology and the positive downstream effects of on the quality of the screening programme itself. In principle, Denmark could be covered by two to three screening units only, however, as anyone would recognise, this is not a popular point of view among the current performing screening laboratories, save the largest units.

Cytology technology and the National Patobank

Today, the Danish screening programme relies only on liquid based cytology (LBC), with the last department implementing LBC in 2014. Approximately 75–80% of all cervical samples are stored in SurePath, whereas the remaining 20–25% are stored in ThinPrep. The reason why in The Horizon Study we exclusively focused on HPV assay performance using samples stored in SurePath was that this technique medium dominates the Danish cervical screening effort, and is the only medium used in our region.

In the early 2000s, computer-assisted reading of cytology samples and use of LBC were gradually implemented throughout Denmark. Our department started reading samples using the BD Focal Point system in 2000, and started using BD SurePath LBC in 2002. One department started using ThinPrep LBC in 2004, and the ThinPrep Imaging System for computer-assisted reading in 2006.

From 1996, the majority of cytology in Denmark has been registered in the National Pathology Data Bank (Patobank), and registration has been virtually complete since 2005. The Danish Patobank is the mainstay of Danish cervical screening. It allows all MDs (doctors) to electronically access a screening result within minutes after the sample is registered. The Danish Civil Registration System (CRS) ensures that every person has a unique 10-digit identifier,

but on top of that all practising MDs have a unique identifier following their person too, so the identification is secure. The Patobank structure allows for a full record of all screening and pathology samples for the patient to be reviewed no matter where or when the sample(s) were taken. This system allows us to investigate many aspects of screening from a scientific perspective, including the consequences of technology changes (6, 8). An example evaluating the consequences of introducing LBC and computer-assisted reading in three large pathology laboratories is given below.

From 1998 to 2007, the cytological abnormality rate, defined as atypical squamous cells of undetermined significance (ASCUS) and above, remained constant in a pathology department using conventional cytology and manual reading throughout the period. The implementation of LBC in two other laboratories, however, changed the dynamics of detection of \geq ASCUS in an age dependent manner (8). Implementation of SurePath LBC was followed by an increase in abnormal cytology in women aged 23–29 years from 4.6 to 6.1%, relative proportion (RP) 1.31 (95% confidence interval (CI): 1.08–1.61). In women aged 45–59 years, on the other hand, implementation of the same technology reduced the prevalence of \geq ASCUS from 2.9 to 2.0%, RP: 0.71 (95% CI: 0.60–0.83). Implementation of ThinPrep LBC was followed by a decrease in abnormal cytology both in women aged 23–29 years, from 7.7 to 6.8%, RP: 0.89 (95% CI: 0.78–1.02), and in women aged 45–59 years, from 3.4 to 1.0%, RP: 0.30 (95% CI: 0.24–0.37). With implementation of imaging-assisted reading, regardless of the brand of technology (SurePath- or ThinPrep-based), the proportion of abnormality increased in the same two laboratories by around 30% in all age groups (range from 19 to 41%).

To complete the analysis, however, we should not only focus on the changed specificity, but also note that the same data for SurePath showed that the sensitivity of detection of disease (cervical intraepithelial neoplasia grade 2 or higher) actually doubled among young women (+104%, 23–29 years), and increased by 59% in 30–59 old women. So in conclusion, implementation of LBC increased the detection of ASCUS or above, but also of histologically confirmed disease above the treatment threshold (presented at ICSN, Sydney, 2012).

Follow up of abnormal findings

Detection of cytological abnormalities must be supported by follow up of the abnormal findings for the screening to have any effect. In Denmark, it is the responsibility of the sample-collecting physician, typically GPs or gynaecologists, to ensure follow-up of abnormal findings. In 2012, 20% of women with abnormal and unsatisfactory cytology samples were not followed up within the recommended time intervals as set forth in the national recommendations. For samples with high-grade squamous intraepithelial lesions (HSIL), 5% were not followed up within the recommended 3 months; 4% were not followed up within 6 months; and 1.3% not within 15

months. For women not followed up according to the recommended schedule, automatic reminders started being sent from the pathology departments to the sample-collecting physicians in February 2012 (5). The programme still has room for improvement in this respect. Nationwide monitoring and annual reporting of these (and other) trends from the Danish Quality Assurance Data Base for Cervical Screening started in 2009 and is increasingly becoming a tool to ensure equal quality of service across the country.

HPV testing in the screening programme

Like in the UK, HPV technology is increasingly being utilised in cervical screening in Denmark. By volume, Hybrid Capture 2 is the most widely used HPV DNA test in Denmark, with Roche's cobas and Genomica's CLART genotyping assays as the second and third largest systems in play.

Three indications for HPV testing are currently recommended in Denmark;

- Triage of women with ASCUS at age ≥ 30 years,
- Test of Cure (control after treatment of dysplasia),
- And the new check out testing at age ≥ 60 years.

Triage of ASCUS and control after treatment of dysplasia with HPV testing were recommended by the National Medicines and Health Authority in 2007 and were gradually implemented nationwide. Our department was the first to start with triage of ASCUS for women aged 30 years and above in 2005 and has used HC2 for this purpose. Another pathology department started using the PreTect HPV-Proofer HPV-mRNA test in 2006 for women of any age and women with low-grade squamous intraepithelial lesions (LSIL). However, as of 2012, NorChip testing is no longer part of the national screening activities due to lack of documentation that it actually provides clinically useful information. Analysis of the outcomes is on-going.

Test of cure as HPV testing of the first cytology sample post conisation is the second HPV DNA testing indication in operation, and is carried out at varying degrees of implementation across the country. No substantial data is yet compiled and analysed as to the effect of this testing; however, we follow closely the experiences from the UK on this.

In the 2012 amendment to the national screening recommendations, a new HPV indication was introduced: check out testing for women aged 60 years or above. This means that women with negative HPV DNA tests at age 60 will not anymore be invited for screening; this is different from cytology-based screening where women would be invited for an additional round at age 65 years. The rationale for implementing the check-out testing is that a negative HPV DNA test result offers the same protection against treatment-requiring dysplasia as two cytology tests taken 5 years apart. This is indeed primary HPV screening and is currently under implementation nationwide,

expected to be completed later in 2014. The choice of HPV technology for execution of HPV DNA check out testing has been widely debated in Denmark. The resulting national recommendations for quality assurance and quality control of molecular HPV testing (published in November 2013 by the Danish Association of Pathologists in collaboration with the Danish Working Group on Molecular Pathology) stipulated that any test used for this purpose must entail a sample-by-sample control for human DNA to ensure the sufficiency of the sample. The rationale behind this is to not risk checking out any women on the basis of an insufficient sample. Though this precaution may seem reasonable, it also means that the currently most widely used HPV DNA test in Denmark by test volume, HC2, is ineligible for this indication. Based upon data from The Horizon Study, we expect that 92–94% of all women tested at age 60 can be “checked out” and not undergoing an additional screening cytology testing 5 years later.

The Horizon Study: Expanding our knowledge and experience on performance of HPV testing of samples stored in SurePath

To prepare for the implementation of primary HPV-based screening, the Copenhagen University Hospital, Hvidovre, undertook The Horizon Study; this was a split-sample study evaluation of four HPV assays in a true routine setting. The rationale behind this study was, in short:

- 1) To obtain relevant experience with HPV technologies in a Danish context,
- 2) To assess the performance of the four assays in a true routine screening setting,
- 3) To assess the laboratory performance of the assays with respect to the reproducibility of test results under routine conditions.

Approximately 6,000 SurePath LBC samples were randomly selected from consecutively received routine samples. All samples were tested with LBC and HC2 (Qiagen, Gaithersburg, MD). Out of these, approximately 5,000 samples with sufficient material were additionally tested with the cobas HPV Test (Roche Diagnostics, Pleasanton, CA) HPV DNA test (cobas), the CLART HPV2 Assay (Genomica, Madrid, Spain) HPV DNA genotyping test (CLART), and the APTIMA HPV Test (Hologic/Gen-Probe, San Diego, CA) HPV mRNA test (Aptima).

Overall, 27% of the unselected samples tested positive on cobas, 24% on CLART, 20% on HC2, 17% on Aptima, and 7% on cytology (4, 9–11). For primary screening samples at any age, the percentages were 25%; 19%; 17%; and 6%, respectively (4, 9, 10). Even at age 30–65 years, the proposed target age for HPV-based screening, the proportions of women with positive primary screening samples were 16% on cobas, 16% on CLART, 12% on HC2, and 9% on APTIMA. Pair-wise comparisons across the assays showed a marked discordance in identification of HPV-positive women, with only half of women testing positive on one HPV assay testing positive also on the other HPV assay (11). On the other hand,

the disagreement between the assays was less striking when restricting the analysis to samples with concurrent cytology-abnormal results ("referral population", often studied by others (12–18)). The simple conclusion to this is that the performance of the assays may seem alike when only evaluating samples from women in follow up for cytological abnormalities, whereas primary screening samples, of which the vast majority is normal on cytology, offers a different challenge. Follow-up data from the study will be reported shortly.

currently suggested for is purpose; cytology, methylation markers, genotyping, p16/Ki67 etc. (19–21). However, while triage may limit the number of women referred for colposcopy following a positive HPV test result, it will only limit the number of women in need of repeated testing if women with HPV-positive/triage-negative results are returned to routine screening rounds. And can we do that? I would argue "YES", but with a small trade-off in the risk (22).

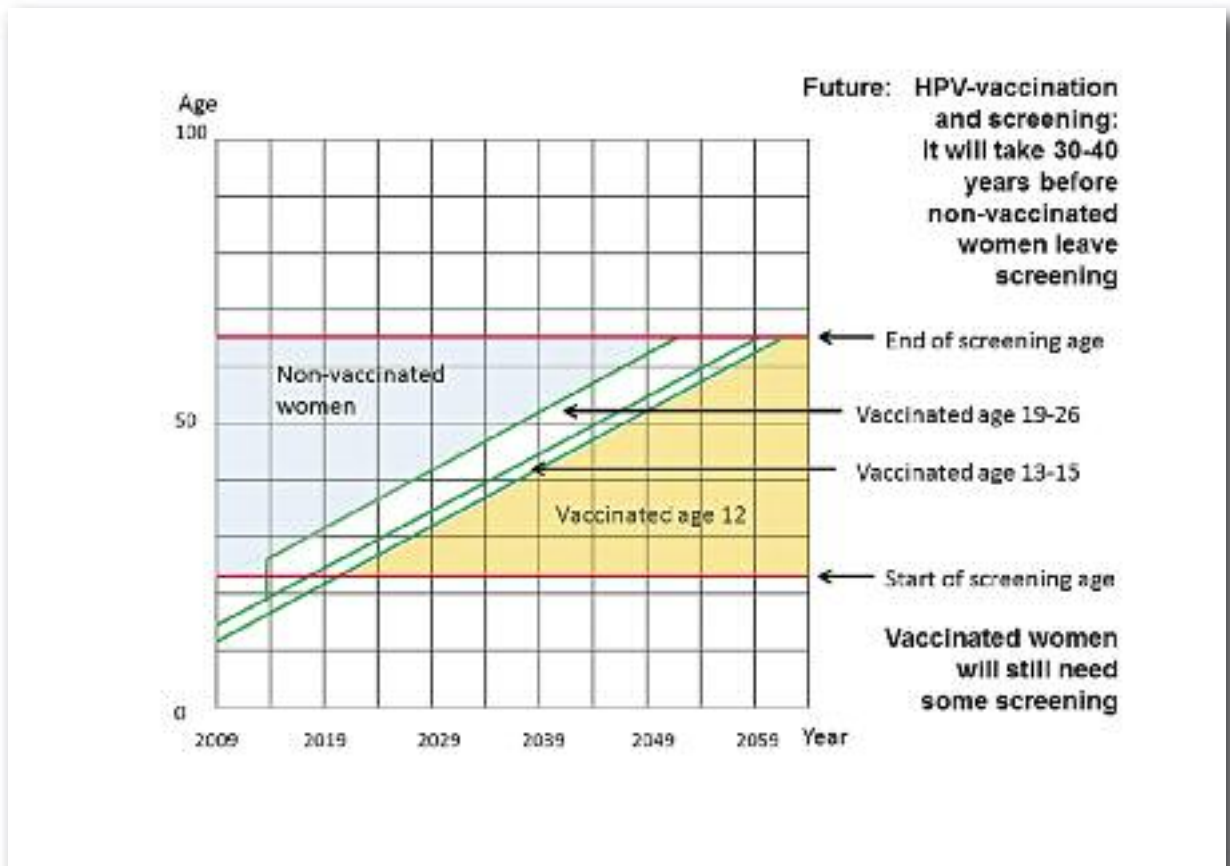


Figure 3. Future distribution of Danish women according to cervical screening and human papillomavirus (HPV) vaccination status. Reproduced from Lynge et al. *APMIS*, 2014.

The Horizon Study data indicate that a shift from cytology to HPV-based screening requires an evaluation of the downstream events following a positive HPV primary screening test. In total, 4% of samples were abnormal on cytology, and, hence, in need of supplementary tests (repeated testing or a colposcopy referral). The proportion of screened women aged above age 30 years in need of supplementary tests at the first round of HPV-based screening was 16% for e.g. cobas (see above), and would thus increase by about four times compared to using cytology. The experiences and data from The Horizon Study on true primary screening leave us with the concern that the proportion of women in need of supplementary testing will be much higher with primary HPV-based screening than with cytology. This will challenge both the health care system with unnecessary re-testing, and the patience of the women.

Hence, triage of HPV positive primary screening samples must be undertaken, and various methods are

The first results out of The Horizon study, particularly the statement that HPV tests are "not created equal", received a lukewarm international reception at the IPV conference in San Juan in 2012. However, several other sites engaging in pilot implementation or pilot trials in routine screening have since observed the same issues with the disagreement in detecting HPV infections between different HPV assays. This is puzzling as the assays were in theory calibrated to detect the same disease causing infections (11).

As a concluding note, HPV testing is, regardless of the discordance between the various assays, superior in detecting cervical disease, so from the point of view of disease detection and protection against cancer, the case for primary screening is clear. The Horizon Study though pointed out differences in the performance between the four widely used assays, and based upon those experiences we now feel better suited to design the best solution for primary HPV screening in our setting.

A Future Challenge: Vaccination will reduce the number of cervical abnormalities, thereby challenging the quality of cytology

The quadrivalent HPV vaccine Gardasil (SP-MSD) was marketed in Denmark in October 2006, and the bivalent vaccine Cervarix (GSK) in September 2007, both to women aged 9–26 years. A free vaccination programme (a nationally sponsored childhood vaccination programme) with Gardasil started in October 2008 for girls born 1993–1995 (13–15 years old), from January 2009 for girls born 1996 (12 years old), and thereafter regularly for girls turning 12 years. From August 2012 to end of 2013, vaccination was offered also to women born 1985–1992 (19–26 years old) as a “catch up” initiative. By February 2013, 87% and 90% of women born in 1993–1996 and in 1997–1998, respectively, had received at least one vaccine dose, and 81%–82% had received all three doses. From January 2014, vaccination can be offered up to the age of 18 years, and women born in 1993–1995 can be vaccinated until the end of 2015.

Given the present distribution of HPV types in the Danish population, and assuming 100% vaccination coverage and 100% vaccination efficacy, 52% of cervical cancers are expected to be prevented with the quadrivalent vaccine. For CIN3, this is 26%. Under the same assumptions, the future nona-valent HPV vaccine is expected to protect against 89% of cervical cancers and 91% of CIN3. It should though be noted that this is the long-term perspective for vaccine-type naive women, and not a scenario expected to be seen within the next 30 or so years.

The full effect of HPV vaccination will manifest itself over the next 30 years. In that period, cervical screening in Denmark has to adapt and cover quite a diversified population: non-vaccinated women; non-HPV naive, vaccinated women; and HPV naive, vaccinated women (Figure 3). Moreover, the proportion of abnormal LBC samples in routine screening will decrease as the HPV-vaccinated women enter screening age, and this might lower the proficiency of cytology screening. If the current cytology is looking for the needle in the haystack, the future is that the needle just became smaller, and the haystack larger.

The superior protection against cervical cancer is of course the main reason for implementing primary HPV-based screening instead of continuing with screening based on cytology. On top of that, a switch to primary HPV-based screening is the obvious response to the challenges cytology may face as a consequence of the vaccination programme.

A Future Challenge: Increasing the participation in the screening programme

Among Danish women with cervical cancer, 45% were not screened in the last 7.5 years prior to the diagnosis (23). The national indicator target for the coverage rate in the organized screening is 85%. Yet, regional numbers slug away ranging from the mid-60's to the mid-70's. Increasing the coverage

from our current regional 76% is a challenge, but is indeed the lowest hanging fruit to pick when it comes to the discussion on improving the effectiveness of the organized screening programme in Denmark.

Currently, women receive an automatic invitation and two reminders. Experiences from this computer algorithm-governed invitational system shows that approximately 10% respond to the 2nd reminder (the numbers are included in the 76% coverage). An obvious extension to this system would be to mail a 3rd reminder and hope that it would generate an additional 3–5% response. However, an alternative strategy is to utilize self-sampling and HPV technology.

To this end, we have engaged in a large pilot/implementation activity offering self-sampling to women who have not attended screening for 4 years or more. Up to 25,000 women will at first be offered self-sampling as an alternative to physician-taken samples. We have pursued an “opt-in” communication strategy with apps and web registration in addition to the more traditional mail-based communication. By utilizing modern communication platforms we hope to make “opting in” easy. And indeed the strategy worked. Here, three months into the implementation, 40% of the women who accepted the invitation responded via the electronic platforms. Moreover, the “opt-in” strategy was chosen to reduce the massive cost of mailing brushes to all non-attenders up front, of which an expected 70–80% would not be returned for analysis. So far, with a current response rate of 25%, it appears that the concerns about a low the participation rate with the “opt-in” strategy in the self-sampling initiative have been unfounded.

We have chosen a dry brush, the Evalyn, as we found it unsafe to ship any sort of sampling liquid to private homes. On top of that, we asked the manufacturer of Evalyn, Rovers from the Netherlands, to embed a radio frequency controlled chip into the handle of each brush to ensure superior patient safety by secure identification. This has the added benefit that we do not have to ask the women to return any paperwork, add labels to the devices, or rely on glued-on barcodes. The identification is in the device.

We do not use the self-sample as a stand-alone diagnostic sample or a substitute for a regular screening sample. We use it to direct otherwise non-attending women for a clinician-taken sample if they are HPV positive, and based upon the thus resulting combination of HPV testing and cytology, clinical decisions for follow up will be made. In other words, self-sampling will become an entry point into the screening. The cost effectiveness of offering self-sampling as an entry point for non-attendees will be part of our reporting later. Detailed reporting from the Copenhagen Self-Sampling Initiative will be presented at EUROGIN, Sevilla, 2015.

Conclusion

The Danish cervical screening is well suited to implement primary HPV screening before the full effect of vaccination affects the quality of cytology. Moreover, given the strong focus on QA/QC experiences from amongst others The

Horizon Study and the national recommendations, we can ensure a smooth transition from cytology-based to HPV-based primary screening without detrimental effects to the quality of screening. Finally, we are, for the first time in the Danish cervical screening history, in a unique position to ensure equal implementation of service across the country to level the current differences — that is, if the political will be present.

Self-sampling will be a dark horse in the future. I foresee a lively discussion on whether women should be offered the choice to take a self-sample or go to the physician's office for a regular cervical screening sample. With almost 450,000 cervical screening consultations reimbursed every year by the Danish national health care system, offering women to take the sample on their own might reduce the cost of the screening programme as some women will prefer to take the regular screening sample themselves rather than going for the GP's office, as well as raising attendance by catering also to women who are currently non-attendees for whatever reason. Very importantly, the aim here is not to replace the physician-taken cytology sample for primary HPV testing and subsequent cytology triage, but to make screening more accessible to all. Accessibility of the screening program is the key word. Our role as a public health care system is to adapt to the evolving world; by meeting the women wherever they are and by technology implementation that benefits quality.

We will continue to evaluate HPV technologies to further our knowledge on the performance of these systems' under Danish conditions, and thereby to ensure a first class screening programme.

CONFLICT OF INTEREST

JB has in the past served as a paid advisor to Roche and Genomica, and received honoraria from Hologic/Gen-Probe, Roche, Qiagen, Genomica, and BD Diagnostics for lectures. He has received funding and/or consumables to carry out assay evaluations from Hologic/Gen-Probe, Genomica, Qiagen, Roche, and BD Diagnostics. He is principal investigator on a study funded by BD Diagnostics.

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Cervical Cancer Screening in Mekelle, Ethiopia, A Pilot Study ...My Experience

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Introduction

My good friend and colleague Dr Julia Palmer wrote an article for Scan in 2012^[1] regarding her experience in Mekelle, Ethiopia. It was always her intention to return to Mekelle and continue the work her team started in November 2011. The plan was to assess different methods of screening such as visual inspection of the cervix after the application of acetic acid (VIA) and the use of electrical impedance spectroscopy (EIS).

In February 2014 with funding from Sheffield Health Action Resource for Ethiopia (SHARE) Women's Health and a bursary from the British Association for Cytopathology (BAC) I was fortunate to be part of the team that attended to evaluate the feasibility of cervical cancer screening in Mekelle.

Cervical Cancer Screening in Ethiopia

In the UK, we take the NHS Cervical Screening Programme (NHSCSP) for granted and, due to its success, cervical cancer is a rare disease, yet still remains the most common cancer in women under 35 years of age^[3]. In 2011, cervical cancer was the 12th most common cancer occurring in women in the UK with 3064 new cases diagnosed and 972 deaths.^[3]

It is difficult to gauge the incidence of cervical cancer in Ethiopia as there is no screening programme or National cancer registry, plus there is generally a low awareness of the disease which means that women tend to present at advanced stages. Cervical cancer is the leading cause of cancer-related mortality in the developing world. It is estimated that there are 268 million African women over the age of 15 years, with approximately 80,000 new cases of cervical cancer diagnosed per year; more than two thirds of these women will die from the disease.^[4,5]

In Ethiopia, cervical cancer is the second most common adult cancer after breast with an incidence of 18 cases per 100,000 population and mortality of 14 cases 100,000 population.^[6]

There is a high burden of other diseases such as HIV, TB, and malaria so these take priority over cervical cancer. It is estimated that 789 000 people are living with HIV/AIDS in Ethiopia.^[7] We are aware that women who are

immunocompromised with HIV/AIDS are more likely to be infected by HPV making them more susceptible to developing cervical cancer rather than women who are HIV-negative^[8]. See Table 1.^[9]

	Incidence	Mortality
Annual number of new cases/deaths	7095	4732
Crude rate	16.3	10.9
Age-standardised rate	26.4	18.4
Cumulative risk 0-74 years (%)	3.0	2.1
Ranking of cervical cancer (all years)	2 nd	2 nd
Ranking of cervical cancer (15-44 years)	2 nd	2 nd

Table 1. Burden of cervical cancer in Ethiopia^[7]

Mekelle is situated approximately 780 km north of the capital city, Addis Ababa in Ethiopia (Figure 1). Mekelle is the capital city of the region of Tigray and has become an economic hub with an educational centre, airport, medical school, teaching hospital and is developing a role in tourism. Based on the 2007 Census, it is estimated that Mekelle has a population of 215,914^[2]. Ayder Hospital is the teaching hospital of Mekelle University and the major tertiary referral centre for the Tigray region. Again Mekelle has no cervical screening or cytology department, but is able to perform visual inspection under acetic acid (VIA) and have access to a colposcope.



Figure 1 Map of Ethiopia

Pilot Project in Mekelle

The project team comprised of Dr Julia Palmer (JP), lead investigator, gynaecological oncologist and lead colposcopist at Sheffield, Mr George Angelopoulos (GA), subspeciality trainee gynaecological oncology, James Cook University Hospital, Middlesbrough and me — Kay Ellis (KE) from Cytology at Sheffield. Another team led by Professor Tom Farrell (TF) attended with the intention of providing educational and practical training sessions in obstetrics and gynaecology.



Figure 2: The Team

The aim of the pilot study was to identify the best way of introducing a cervical screening strategy and training programme, taking into account limited resources, at Ayder Referral Hospital, Mekelle. We intended to recruit 100 consecutive women, all who had been consented and were attending the gynaecological out-patients department at Ayder Hospital. Women were excluded if they were actively menstruating, pregnant, diagnosed with cervical cancer, or if they were younger than 21 years or known to be older than 65 years of age.

Specific objectives included:

- Feasibility of performing conventional Papanicolaou smears to include correlation between the opinions of a UK trained and qualified cytologist and pathologist based in Mekelle.
- Correlation of conventional smears as compared with liquid based cytology, to be processed in England.
- Human papillomavirus (HPV) testing and genotyping for HPV 16, 18 and other high risk types, to be processed in England.
- Accuracy of VIA performed by British Society for Colposcopy and Cervical Pathology (BSCCP) accredited colposcopists and local equivalent medical staff using cervical cytology/biopsy as end point.
- Accuracy of colposcopy performed by BSCCP accredited colposcopists and local equivalent medical staff using cervical cytology/biopsy as end point.
- Accuracy of Zedscan™ performed by BSCCP accredited colposcopists and local equivalent medical staff as compared with VIA and colposcopy.
- Correlation of histopathology opinion between a UK trained cytologist and local pathologist in biopsy and large loop excision of transformation zone (LLETZ).

Women who were thought to have high-grade cervical intraepithelial neoplasia (CIN) would be treated at their appointment so in effect a 'see and treat' policy would be in operation facilitating a one stop clinic approach.

Visual inspection under acetic acid (VIA) is a method to detect premalignant changes in the cervix. VIA is usually utilised where women have limited or no access to cervical cytology screening, usually in resource poor countries such as India and sub-Saharan Africa. Dilute acetic acid is applied to the cervix and any abnormal areas of the cervix turn white. These areas are termed aceto-white and can be quite easily visualised by a trained practitioner. VIA is beneficial as little equipment is required, it is cheap and non-invasive for the woman, can be performed in rural health clinics, plus it provides instant results. A similar test, visual inspection with Lugol's Iodine (VILI), may also be performed. Lugol's Iodine is applied to the cervix (VILI) and areas of epithelium that are iodine negative may indicate a premalignant condition^[10,11].

A research group in Sheffield has been investigating the use of EIS (ZedScan™) as a method of identifying high-grade cervical intraepithelial neoplasia (HGGIN)^[12,13,14,15]. In simple terms by measuring the electrical current in different positions on the cervix, the ZedScan™ informs the user whether there is HGGIN present. It is a battery hand held device with the base connected to a lap top so that the data can be downloaded for analysis. A sheath is placed over the probe, the business end of the scope and is applied to cervix where up to 12 measurements are taken. The team in Sheffield have published a number of papers evaluating the ZedScan™ in detecting CIN and, as stated earlier, are planning to use it as part of the pilot programme in Mekelle.

Julia Palmer wrote the study proposal in June 2013 and submitted for approval at Sheffield Teaching Hospitals NHS FT and Ayder Referral Hospital, Mekelle. Patient information leaflets and consent forms were also written and forwarded to Mekelle so they could translate into the local language. The proposal was approved after many e-mail conversations mainly surrounding issues of removing patient tissue out of Ethiopia for further testing. As a result, we agreed that we would not ship back any human material to the laboratory in Sheffield and the LBC and HPV testing aspect of the original pilot would to be omitted from the study.

Our visit dates to Mekelle were agreed for two weeks dating from 24th February 2014. The flights and accommodation were booked and everything was set for the visit.

The visit

The team met up at Heathrow airport on Friday afternoon and we finally arrived at Mekelle via Addis Ababa on Saturday afternoon. We were expecting to be met at the airport but nobody was there to greet us. Perhaps in hind sight this was a sign of what was to come. We eventually managed to arrange two taxis to take us, and our luggage to the Hotel which was to be our base for the next two

weeks. The taxis had definitely seen better days and were held together by gaffa tape. The scene reminded me of the cars in TV cartoon series *The Flintstones* and I was expecting my feet to go through the floor of the car to help it along! I was very pleasantly surprised with our room. It was a big room with two double beds, widescreen TV, cupboards and wardrobes plus a decent bathroom — better than some 'luxury' accommodation I have had in India! The problem we had was that the only available electrical sockets that worked were in the bathroom which meant that we were fighting over what to charge next. Sadly this meant no TV so reading was certainly on the agenda.

Monday

It was agreed we would be picked up at 9am to be taken to the hospital to start our study. We had a telephone call at 8am to say that there was someone in reception waiting to pick us up. We were dropped off at the main entrance of the hospital. The hospital was quite impressive from the outside and looked more like a hotel. The hospital reception was clean but busy. A young doctor greeted us and took us up to the office of the Dean. The Dean was away at a meeting in Addis Ababa, but every cloud has a silver lining and we were at least able to leave all our equipment and bags there.



Figure 3: Ayder Hospital

We asked to be taken to the gynae out-patients department (GOPD) to sort out the equipment we needed for the study. No-one was particularly helpful. JP had requested that the colposcope was available for use in the GOPD but no one seemed to know anything about it. The pathology laboratory was situated in the same block and we went there to drop off my 'bits and bobs'. I took text books, marker pens and pencils, old BAC conference bags and SCAN plus conventional glass slides. I was introduced to the Head of the Department of Pathology and Assistant Professor. When JP came before in 2011, the lead pathologist was a single-handed pathologist covering a population of over 4.5 million. He has been at Ayder for four years and has now been joined by two trainee pathologists.



Figure 4: Reception at Ayder Hospital

We were taken to meet the Medical Director who had actually gone to the hotel to collect us. It appeared that he knew nothing about our visit but was very polite when he listened to our plan to pilot different cervical screening strategies and obstetric and gynaecology training for the trainees. He assured us that he would look in to it and make sure that we had everything we needed. He was clearly very proud of his hospital which had opened in September 2008. The hospital has 450 beds and has an emergency room, departments of Internal Medicine, Surgery, Gynaecology and Obstetrics, Paediatrics and Dermatology. There are surgical theatres, delivery rooms, adult intensive care unit, special care baby unit, out-patients, pharmacy, pathology laboratories and an x-ray and imaging departments.

We were shown around the hospital and saw the dialysis unit, obstetric unit and the intensive care unit. The hospital was full of people waiting around but we did not see many doctors or nurses. In the delivery area, women were surrounded by other women who were probably there to help them with their birth. The hospital was relatively clean in the areas we saw, but there was certainly a very distinctive smell which is difficult to describe. With assurances that everything would be OK tomorrow we called it a day at lunchtime

Tuesday

We were picked up in a minibus to go to the hospital together with a team from Germany who were working in hospital financing. TF and his team went to the Obstetric unit. JP and GA went to GOPD to set up and commence the pilot study. I went to Pathology and was shown around the department — well two rooms by the senior technician.

The laboratory processes approximately 2,000 histology specimens per year and 5,000 non-gynaecological samples. I was quite impressed with how well-equipped the laboratory was. They had a carousel processing machine, two embedding centres and two microtomes. All the equipment was in the same room with the only ventilation being provided by an open window. Staining was performed by hand. The senior technician asked me how often we changed solvents on our processing machines and he showed me the sheet next to the carousel processor showing that the solvents had last been changed in November 2013. They used disposable microtome blades and the current blade had cut 50 blocks — 'they are an expensive resource!' The lead pathologist had performed some cervical cytology but was obviously very experienced in screening non-gynaecological cytology samples. I had taken some conventional smears with me for training and to refresh my interpretation of direct smears.

JP soon came in to the laboratory and informed me we were leaving for the day. The colposcope had still not arrived in GOPD, no doctors had turned up for training, and there were no patients to be seen. The lead pathologist tried to sort things out and arranged to meet us at lunchtime. We were taken to a restaurant and met the Dean of the university. The Dean

apologised profusely for the lack of communication and that things had not been organised. He said he would organise adverts on the local radio to help with recruitment to the pilot. I had mushroom pizza for lunch thinking this would be safe to eat. The food had the same smell as the hospital and I did not want to appear rude by leaving my food so I ate some. Later that day I was violently sick and I was ill through the night. Some of the team (not JP) suspected this to be a result of the infamous and fantastic St George's Ethiopian beer.

Wednesday

I spent the whole day in bed or in the bathroom, as suspected not an illness due to St George's amber nectar. JP returned and told me they had seen 20 women. They had taken 12 cervical samples and these had been left in the laboratory for staining.

Thursday

I went straight to the laboratory. The senior technician had kindly stained the slides for me. There was a sheet for each woman that had her study number on with her clinical details plus colposcopic impression with VIA and ZedScan™. I turned the page over so my reports would not be biased by their findings in colposcopy. I screened the slides first and the local pathologist was planned to screen them independently. We were to compare our results and would go over any discrepant slides on the multi-headed microscope.

Unexpectedly JP came in to the laboratory and informed me the study was closed down. I was to leave everything there and we were to leave. The research lead who had been away in Addis Ababa had finally turned up in clinic and said that he would not give clearance for the study despite clearance from the Medical Director and all the correspondence between the two institutions which he had been included in. He was very aggressive and threatening in front of a room full of patients. JP was obviously upset and frustrated with this turn of events as we all were. It was particularly disappointing as there were about 40 women waiting to be screened. The lead pathologist again was the peacemaker trying to sort out the mix up but as the research lead was threatening to report us for research fraud and have us detained at Addis Airport, there was no turning back. The lead pathologist was very apologetic and was trying to persuade us to stay. TF and GA met with the medical director, lead pathologist, and research lead to talk things through. JP was too angry and upset to attend as the research lead had left her feeling physically threatened as he had been abusive with aggressive body language. Again the research lead was aggressive to TF and GA threatening to report our group to the Authorities.

We left the hospital and went directly to the Ethiopian Airways office to bring forward our flights by a week. Our spirits were down and we were extremely frustrated. I was ill again that night!

Later that evening the lead pathologist attended the hotel and tried to convince us to stay and complete the project.

The team decided that it was best to leave on this occasion.

Conclusion

The whole event had been very frustrating and not to mention very expensive. It was disheartening to leave the hospital and the women who had attended for screening without completing our task. JP's comments were that altruism can only be successful if there is commitment from both parties. All the paperwork had been completed and approved but one individual had managed to stop the programme simply because he wanted to.

Apart from being ill, I have made a new friend and contact with the lead pathologist. He and his team were keen to learn and we have since exchanged e-mails and presentations. I am hoping he will write an article for a future edition of SCAN as his help and thoughtfulness were invaluable. As aforementioned every cloud has a silver lining and the lead pathologist was excellent and highly regarded and respected by all of our team. If only things had been different...

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New BAC Executive Members

Our two most recent BAC Executive Members who have taken up their roles are Jackie Jamison and Claire Geary, two well known names in UK Cytology. They have replaced Mina Desai and Melanie Buchan, and we owe a debt of thanks for all their work whilst on the BAC Executive. Mina has agreed to take on the Editorship of Cytopathology, whilst Melanie has moved onto new challenges outside of cytology. We wish them both well!



Jackie Jamison

Jackie is employed by the NHSC Trust as the Consultant Head of Service for the Cellular and Molecular Pathology Department which includes cytopathology, histopathology, molecular pathology and the mortuary. She is the HBPC for the Trust, and also the QA Pathology Lead for the N.I. CSP. She is particularly interested in Research and Development

and was the principle investigator for N.I. HPV prevalence study and has several on-going research projects involving cytopathology and the use of molecular technology in cancer diagnosis and treatment. Jackie likes visiting Mersault (Burgundy) with her family and 2 grandchildren. She also goes to Co Kerry twice a year with her family as they love to surf and body board whilst she sits on the beach with a flask of tea (well it is Ireland !!!)

Claire is a Consultant Biomedical Scientist in Cytology and Hospital Based Programme Co-ordinator for Addenbrooke's Hospital (Cambridge University Hospitals NHS Foundation Trust) and Hinchingsbrooke Hospital, Huntingdon. Her key areas of interest are training/education and improving the awareness of the HBPC role. Whilst Claire has



Claire Geary

been in post at Addenbrooke's for eight years as a consultant scientist in the Newmarket based cytology lab, her background experience is of a variety of district and teaching hospitals across the UK. This has brought insights

to the challenges of engagement, communication and team working across organisations to deliver a safe and effective cervical screening programme. The lab has recently become part of a network under The Pathology Partnership which covers the Cambridgeshire, Suffolk, Norfolk, Hertfordshire, North East and Mid Essex areas — approximately 40% of screening in the East of England.

When not at work Claire enjoys running (first half marathon soon) and her husband's baking — yes the two are related!



Dr Ashish Chandra

In addition, we are delighted to announce that, following the recent call for nominations for two new BAC Executive members, that Dr Ashish Chandra and Mrs Helen Burrell have been nominated and agreed to stand on the Executive. Both Ash and Helen have many years of experience in cytology, and will be well known to many in the

BAC. Ash, based at Guys and St Thomas' Hospital, London, has helped organise many of the previous BSCC meetings, and we are grateful that he has continued to do so for the BAC, with the most recent being the very successful one day tutorial held only last month. Helen has been Manager of the South West Cytology Training School in Bristol for over 10 years, and has vast experience particularly in cytology teaching, but also in HPV testing. We are very grateful to the Drs Karin Denton and Fraser Mutch, the two BAC Exec members standing down, for all their work and dedication in helping getting the fledgling BAC off the ground over the last three years. They will be a hard act to follow, but both Ash and Helen will be a great asset for the BAC. Our two new Executive members will formally take up their new role after the ASM in October.



Mrs Helen Burrell

BAC Meetings — Past, Present & Future

Alison Cropper, chair, BAC meetings sub-committee

The 2014 BAC tutorial was this year held in London at Guy's Hospital on Friday 11th July. The BAC is indebted to Dr Ashish Chandra for organising and hosting the event which was attended by over fifty delegates.



Ashish Chandra

The first invited speaker of the morning was Dr Anna Green from Guy's Hospital, London, who gave a most informative talk about Cytology and Carcinoma of Unknown Primary (CUP). The discussion revealed the range of cases in which cytology was the sole means of ascertaining the primary site. It also emphasised the importance of clinical correlation with morphology and ancillary testing including gene sequencing for various tumour types.



Dr Anna Green giving lecture

This was followed by equally interesting presentations from two overseas speakers, Drs Darshana and Nirag Jhala, from the University Hospital of Pennsylvania, USA. Both spoke about areas of special interest to them .

Dr Darshana Jhala about EUS FNA of the Pancreas whilst Dr Nirag Jhala presented three short talks on FNA of liver, kidney and adrenal gland. The presentations were lively and interactive dealing with the diagnostic algorithmic approach to onsite assessment in the EUS suite.



Dr Chandra with Dr Nirag and Dr Jhala

After a buffet lunch delegates had the option to choose two from four microscopy workshops, held in the medical school microscopy classroom:

- Urinary tract cytology — Dr Darshana Jhala
- Serous effusions — Dr Mufaddal Moonim, London
- FNA pancreas — Dr Darshana Jhala
- FNA liver, kidney and adrenal — Dr Nirag Jhala



Dr Jhala in workshop

Delegate feedback was mostly very good or excellent, with comments received such as

- 'A highly useful day event which included hands on consultant teaching from the UK and abroad. A huge variety of cases in the workshops which was very

interesting. Thanks to the BAC, Mr Truc Nguyen, Biomedical Scientist

- 'Quality and quantity of slides was great. The presenters were very open and helpful with answers on our questions', Dr Tinka Mohar Hajnsek, Slovenia

Presentations from all speakers can be found in the members' section of the BAC website.

At the time of going to press the Meetings sub-committee are working hard on final preparations for the bi-annual BAC conference, being held at the Crowne Plaza hotel in Birmingham, October 9–11th. I would encourage you all to attend but as this edition of SCAN may well come out at about the same time as this meeting I would be a bit too late!

A varied scientific programme has been put together covering many aspects of both gynaecological and diagnostic cytology, and registrations are approaching the 100 mark. We are hoping to attract around 150 delegates, and it would be great if we could exceed this figure as there won't be another BAC conference for two years after this. The BAC AGM will be held during the conference and a full conference report will be given in the next edition of SCAN.

In 2015 we are planning another spring tutorial and a scientific day meeting / AGM in the autumn, details of which will be posted on the website as soon as we have them confirmed. Both are still in the planning stages so if you have any ideas and suggestions for topics you would like to see included please do get in touch, e-mail kay.ellis@sth.nhs.uk

Finally, some exciting news about events in 2016 — the BAC is pleased to announce that we will be hosting the EFCS (European Federation of Cytology Societies) congress meeting here in the UK.

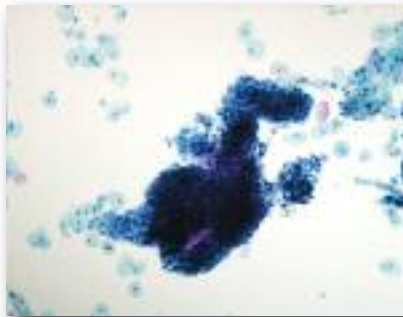
The dates will be 2nd to 5th October 2016 and the host city, chosen by the BAC, is Liverpool. The conference venue will be the spectacular new Liverpool Arena and Convention Centre (ACC), so save the dates in your diary and look out for further information on the BAC website.

This is not only is an excellent opportunity for the UK to showcase all that is good about cytology in the UK, but is also an opportunity for our European colleagues to share what is happening in their countries. There will be ample opportunity for proffered papers and posters so get your thinking caps on and start planning now!

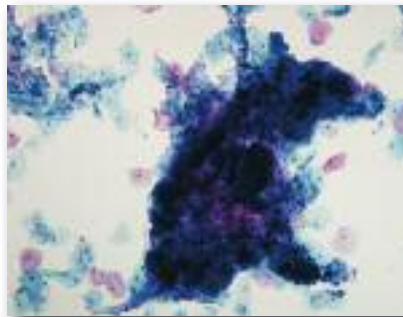
An organising committee is currently being established, to be chaired by Dr Paul Cross, and a sub-committee, chaired by Dr Mina Desai, will put together the scientific programme, so any suggestions you have please e-mail mina.desai@cmft.nhs.uk

We want to attract not just delegates from the EFCS member countries but our own members even more so, so please make every possible effort to be there — opportunities to attend international conferences on our doorstep do not come along very often for most of us so this is a chance not to miss!

Cyto(ani)morphology



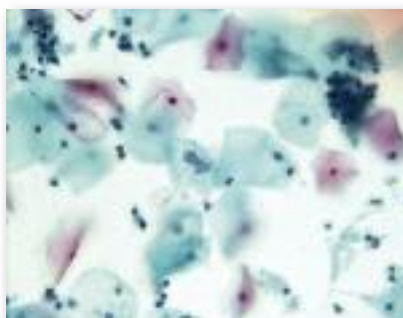
cartoon dragon



dog or fox



rabbit



heart shaped nuclei

Source: Sue Mehew

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(Summer 2014)**



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Please remember to make a copy of
everything before it is sent — there
have been one or two losses in the post.
Thankyou

CEC News – Autumn 2014

Jenny Davies

A very short report as the scheme continues to tick along nicely, with book submissions and JBLs being sent in on a regular basis. Perhaps a more direct approach may be necessary to find out how many active members we still have in the scheme. I will liaise with membership to get a more accurate view. A few of you a very active and I know you all by name which is rather nice, and others complete over a longer term. I know that with current changes in the screening programme, time for CPD activity can be limited.

If you are in a region that currently has a vacancy for a Local Officer, please do send books directly to me or an officer in a different region if you prefer.

When you submit your CEC book for validation, if you do not know your BAC membership number, I can chase up your records with Christian, so don't worry about that for the time being.

Remember — you can still transfer to the new scheme if you have an old book and are a current member of the BAC. The new scheme rules are much more flexible.

Well done once again to everyone participating in the scheme, please keep it up.

Journal Based Learning

Now on to this issue's JBL exercise. **12 questions — 20 credits** (marks are stated next to each question).

This particular one is more in depth and a topic rather close to home; it has therefore been very interesting to set. It relates to FNAC and molecular studies of metastatic breast cancer. *Don't be put off by the apparent complexity of the paper, even if you don't do non-gynae. Cytology (I don't either!). You will be able to find the answers.*

For submission, same instructions as before — photocopy the page and send your answers to me, or your Local Officer, for marking — there is no need to send your book.

Please try to do the JBLs as they come up in each issue of SCAN. JBLs more than 12 months old should be considered closed. Only one submission of each JBL will count.

Remember to keep a copy. Please include your name, BAC membership number, and as we are not receiving your book, your return address

Membership Update

Louise Smart

Chair, BAC Membership Subcommittee

The BAC membership remains healthy with a total of 587 members at the beginning of June 2014, comprising 10 honorary members, 248 consultant medical/consultant BMS members, 316 BMS/cytoscreeners and 9 pathology trainees. We are continuing to welcome new members both from the UK and overseas. As well as receiving Cytopathology and SCAN, as members you have the opportunity to participate in the CEC scheme, are offered preferential registration rates for scientific

meetings and you also have access to additional resources on the website including presentations from recent meetings that you may have missed — spread the word!

As mentioned in the previous edition of SCAN, if you are unsure of your number please contact Christian Burt at mail@britishcytology.org.uk
mail@britishcytology.org.uk

Metastatic Breast Cancer: mechanisms and opportunities for cytology

D. Martins *et al*, *Cytopathology* 2014, **25**, 225 – 230

1. What proportion of node-negative patients ultimately die of metastasis, despite being designated “metastasis free”? (1)
2. Define the term “angiogenesis” (1)
3. What is “Twist” and how does it affect tumour growth? (3)
4. What is the influence on tumours that express both E- and P-cadherin? (1)
5. What is EGFR and how is it associated with human cancers? (3)
6. In relation to metastasis, what is the difference between Oestrogen receptor positive breast cancer, and lung or pancreatic cancers? (2)

-
7. How do "gene signatures" feature in metastasis? Give an example. (2)

 8. Why have the authors advocated use of FNAC for monitoring metastasis? (1)

 9. What is the incidence of breast tumour receptor conversion, with what implications? (2)

 10. Concerns have been expressed about the use of FNAC to study ER, PR and HER2 markers. What are they? (1)

 11. Why is HER2 testing not recommended on cytological specimens? (1)

 12. What is the authors' preferred method of sample collection and why? (2)

20 marks available (marks per question in brackets)

Name..... CEC number (if known).....

CEC Scheme Sponsorship

On behalf of the BAC Executive, and I am sure all the members, I would like to express my sincere thanks to the following companies for the loyal support they have shown over the years in the development and growth of the CEC Scheme.

<p>Pioneer Research Chemicals Ltd Julie Jarman Tel: 01206 791781 e-mail: sales@pioneerresearch.co.uk website: www.pioneerresearch.co.uk 2013/14</p>	<p>Carl Zeiss Ltd (Paul Southey) 15 – 20 Woodfield Road Welwyn Garden City Hertfordshire AL7 1JQ Tel: +44 1707 871200 e-mail: micro@zeiss.co.uk website: www.zeiss.co.uk 2013/14</p>
<p>Source BioScience Healthcare Wilma Anderson Tel: 0115 973 9012 e-mail: Wilma.Anderson@sourcebioscience.com website: www.sourcebioscience.com 2013/14</p>	<p>Hologic (UK) Jo Frost Tel: 01293 522080 e-mail: ukreception@hologic.com website: www.hologic.com 2013/14</p>

Membership Details

Please email or write to Christian Burt if any of your contact details change.

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The UK Cervical Screening Programme — what does the future hold?

Dr Paul Cross

When I started in Cytology in the dim mists of the early 1980's, the labs I worked in within the CSP were relatively understaffed with backlogs of conventional papanicolaou smears of at least 8 weeks, if not more. Automation, apart from stainers, was non-existent. Many labs did not even use computers. Morale was low, and quality was highly variable. Cytology was usually the Cinderella area of Cellular Pathology, with often little real interest from many pathologists, and often other laboratory staff or managers. Training and education was patchy and not always wanted by staff or the managers. Phrases such as *"what changes in cytology, so why do you need training?"* and *"microscopes don't wear out, so there is no need to replace them"* were quite commonly heard.

Much has changed since those days. High profile laboratory failings such as the ones at Inverclyde and Kent and Canterbury precipitated a major cultural shift in the development of a robust QA process. The development of the cytoscreener and biomedical scientist consultant (BMSC) roles were identified, with a proper training and exam process, and these helped develop a far better trained CSP workforce. It also allowed, with the IBMS and RCPATH blessing, the development of the Conjoint Board and the formalisation of the BMSC role and the acceptance of non-medical staff being allowed to sign out abnormal (as opposed to negative) cervical cytology reports. The move to LBC methodology, the introduction of HPV testing, the inextirpable move to laboratory mergers and rationalisation, with the Carter report in mind, have all been introduced. Backlogs, with a 14 day turnaround time, are essentially non-existent. We cannot move within the CSP's for QAT's, CPA, EQA, IQA, and KPI's (and any other acronyms you can find!)

But is the NHS CSP programme actually better? The answer has to be yes — doesn't it? There is no doubt that we have a far better quality assured programme with far better trained and educated staff working within it. The acceptance that others than pathologists can report out abnormal cytology was ground breaking, and has allowed the development of the BMS non-gynaecological cytology role and histology cut-up and now the histology reporting pilots.

So what, if any, is the problem with the CSP? The programme in the early 80's worked to a fairly simple national guidance. It was, and never has been, applied consistently in all parts of the country. It was national only in that it covered the whole UK. The political split-up of the UK has led to a divergence of the CSP programmes, with

Scotland delivering the most variation, and Wales, Northern Ireland and England staying relatively similar. The emergence of HPV testing, and now pilots of HPV primary triage with reflex cytology (rather than the current primary cytology and reflex HPV testing) will, and is, leading to dramatic falls in cervical cytology workloads that require cytological interpretation. The rise of automated cytology screening devices has also led to a reduced need for human intervention within cytology. The CSP workload, and workforce, is declining rapidly. Many labs would not dream of training new cytoscreeners given these factors.

The complex, now 5 page, management protocols of the post HPV CSP are highly complex and leading to much laboratory, let alone clinical, confusion as to what pathway a woman should be following. It is almost an everyday occurrence now to try and resolve what is the appropriate recall and management for a woman, with many a clinician being highly confused, which can result in duplication or unnecessary investigation or even treatment. The programme has evolved enormously in many ways, but confusion in many areas is far greater than ever.

And what role will those laboratory staff left in the CSP have in 5, 10, 15 years' time? The roles will be very different, possibly with fairly minimal direct cytology being looked at. It will perhaps be a far more molecular based service, with development of HPV and related type testing and other markers yet unknown to diagnose, triage and manage women with cervical abnormalities.

So what will happen to the CSP in the future? Less samples, less dedicated cytology staff, less CSP labs; more reliance on HPV methodologies, and less cytology screening requiring CSP interaction as the HPV vaccinated numbers increase. Laboratory mergers have led to a separation of gynaecological from non-gynaecological cytology and histology roles, and a decline in cytology skills in general. Non-gynaecological cytology as a tool and discipline has suffered, and we must not hope mortally so. The professional challenge, for all of us involved in the CSPs, is to ensure that the programme does and can deliver its aims of reduction of cervical cancer by detection of pre-cancerous change. We must transform the laboratory roles and help staff through these changes and retain a high quality trained and motivated workforce through it. That is the challenge for all us, individually and professionally. Time will tell if we get it right or not, but failure not to get it right it could damage cytology in the UK permanently.

Case Study 1

Dr S L Williamson and Dr J D Hemming

Dept of Pathology, Queen Elizabeth Hospital, Gateshead, Tyne and Wear. NE9 6SX

Clinical Details

The patient was a 64 year old woman with a previous history of a screen detected breast cancer presenting with enlarged axillary nodes to the breast clinic. One of the nodes was aspirated for cytology in the one-stop breast clinic.

Below are images 1–4 from one of the air dried slides (MGG) and one of the wet fixed slides (PAP).

What is the diagnosis?

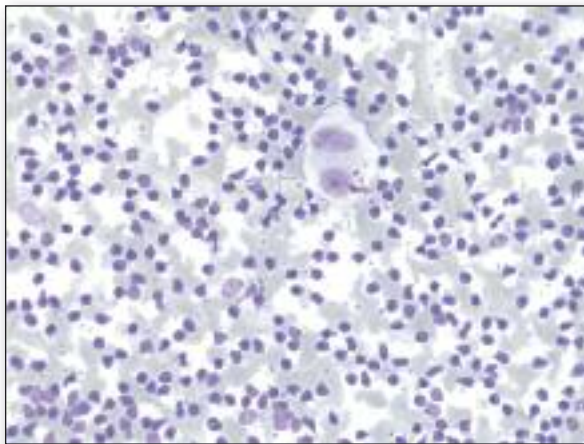


Image 1.

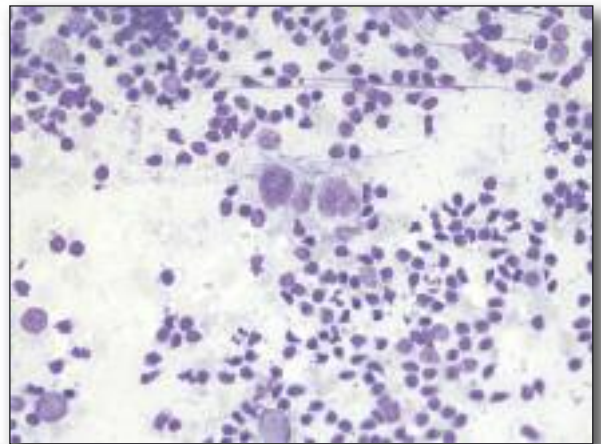


Image 2.

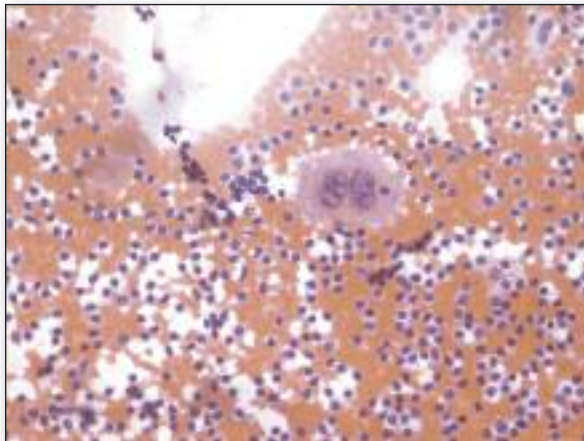


Image 3.

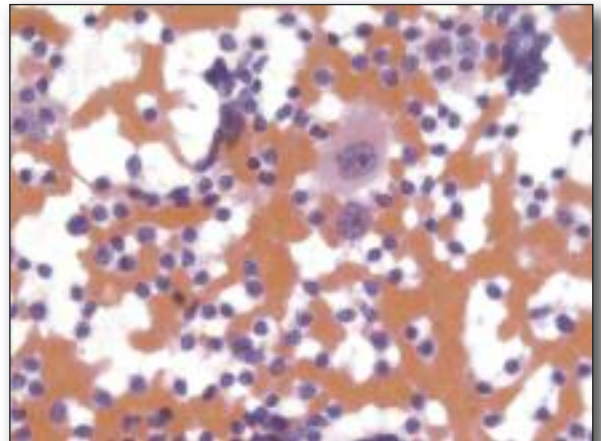


Image 4.

Case Study 2

Dr J D Hemming

Clinical Details

The patient was a 42 year old woman who presented to the symptomatic breast clinic with palpable breast lumps. Mammography and ultrasound examination revealed three well circumscribed lesions all scoring P2, R2 and U2. All three lesions were aspirated for cytology for reporting in the one-stop clinic. Core biopsies were performed at the same visit.

Below are images 1–3 from one of the air dried slides (MGG) and one of the wet fixed slides (PAP).

What is the diagnosis?

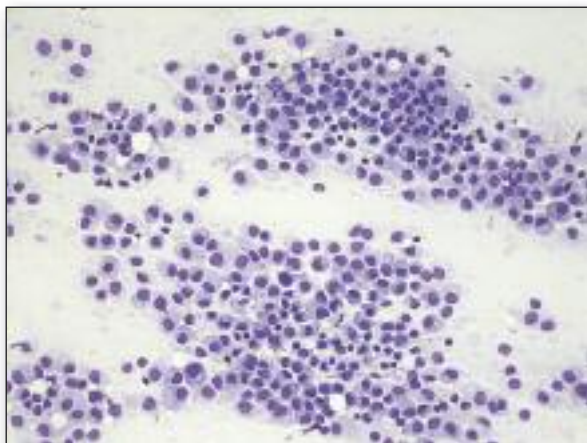


Image 1.

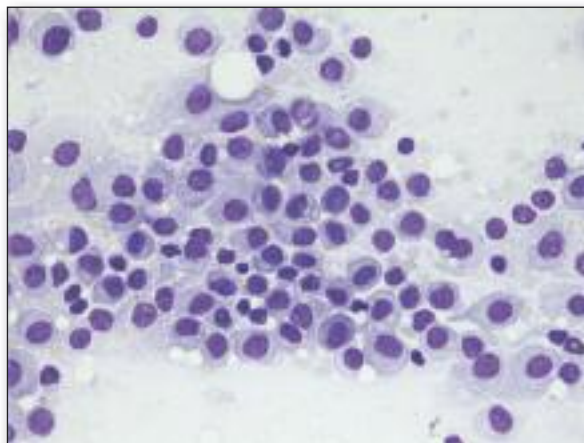


Image 2.

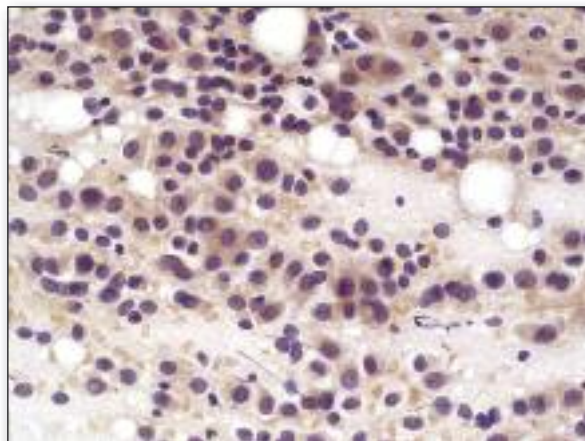


Image 3.

Case Study 3

Dr J D Hemming

Clinical Details

The patient was a 35 year old woman who presented to the symptomatic breast clinic with a cystic lesion in her right breast. She was five months post-partum but not breast feeding. Ultrasound revealed a 6mm cystic lesion in the right upper inner quadrant. This was aspirated for cytology in the one-stop clinic. Core biopsies were performed at the same visit.

Below are images 1–3 from one of the wet fixed slides (PAP).

What is the diagnosis?

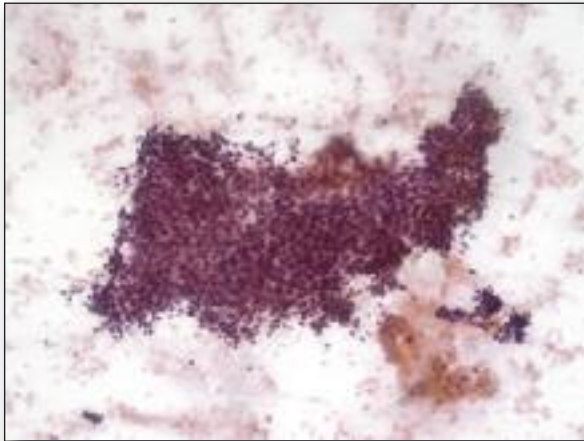


Image 1.

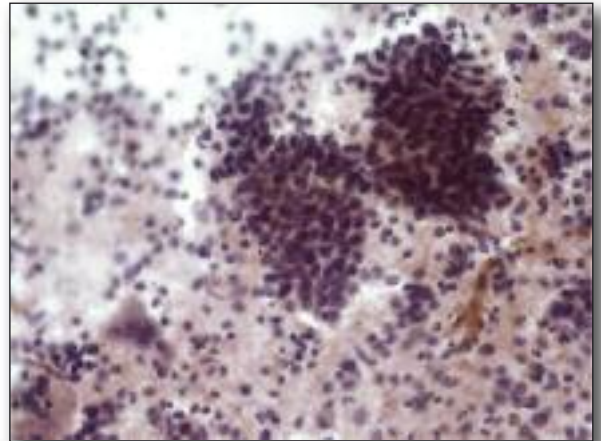


Image 2.

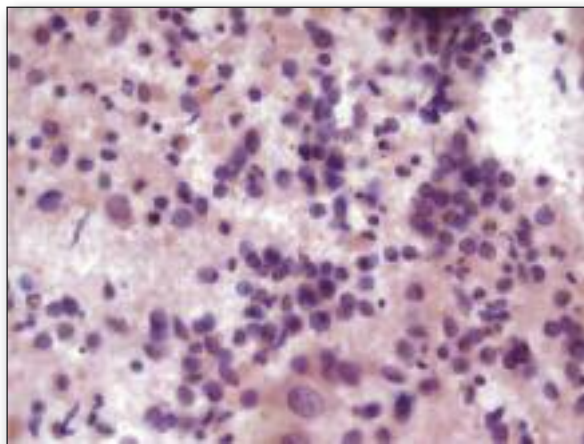
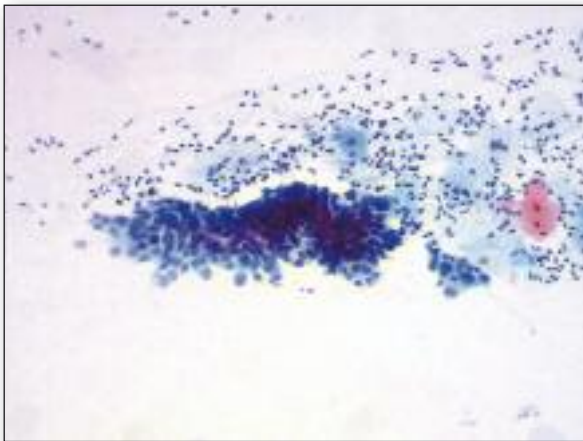


Image 3.

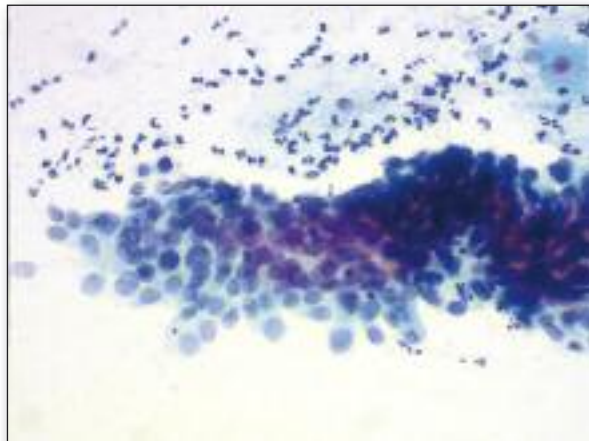
Quiz — Conventional cervical cytology

Marilyn Betchley, Adelaide Pathology Partners.

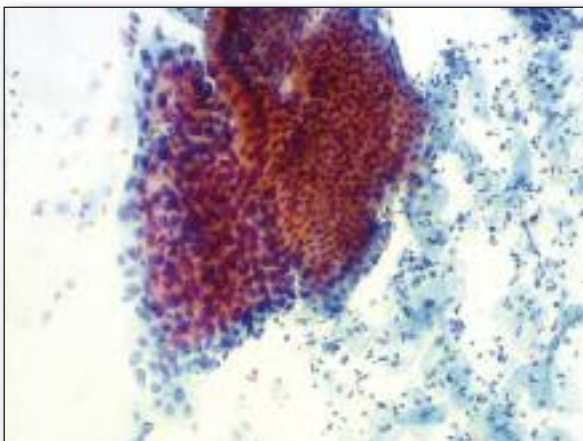
What do you see? Until scrutinised on a higher magnification, groups and sheets of cells may appear deceptively similar. How many of our LBC readers can still recognise conventional PAP Cytology?



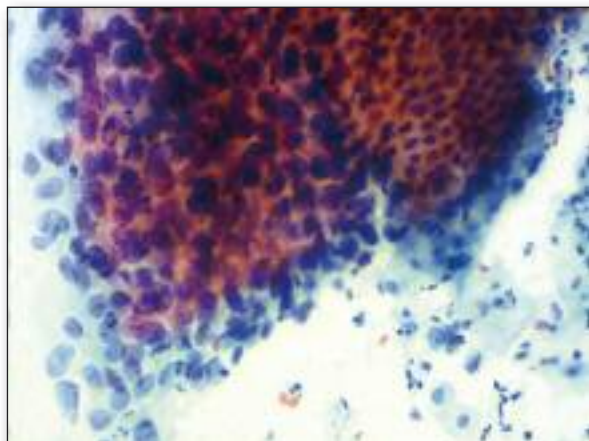
Case 1 x 10



Case 1 x 20

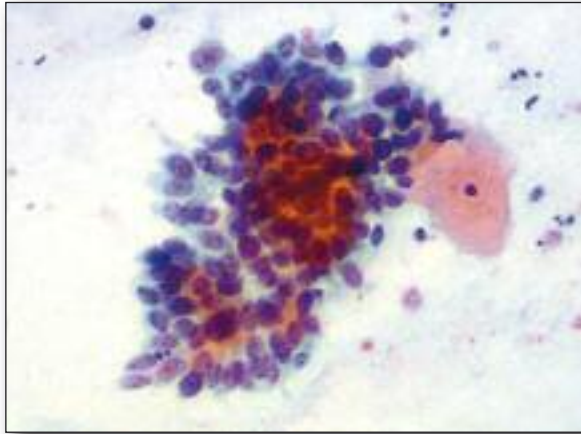


Case 2 x 10

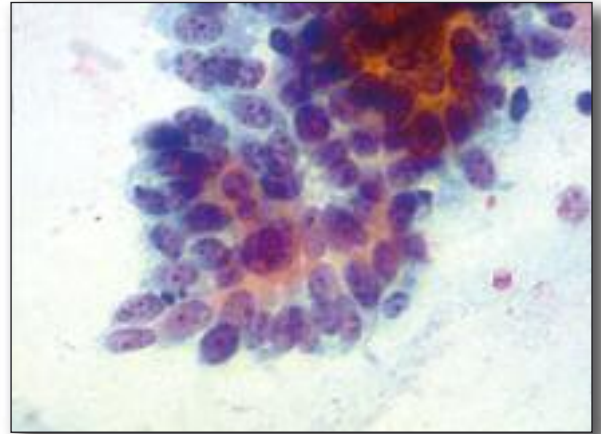


Case 2 x 20

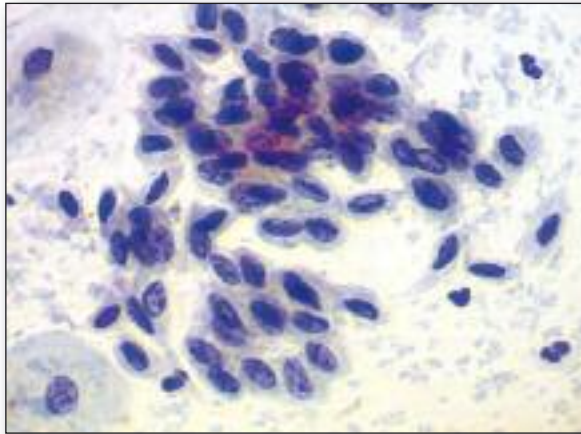
Quiz continued overleaf



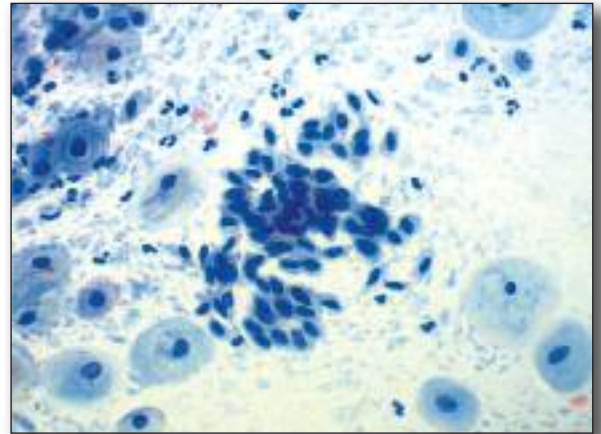
Case 3 x 20



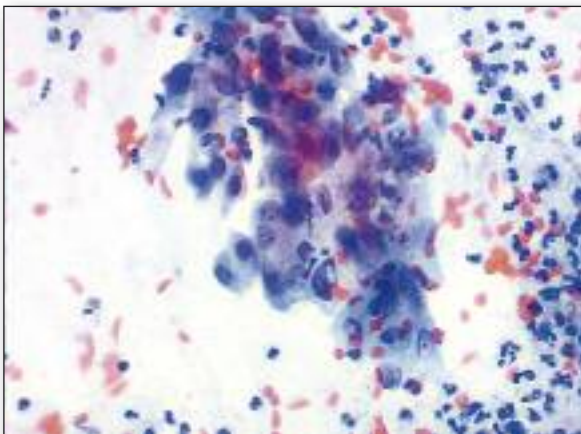
Case 3 x 40



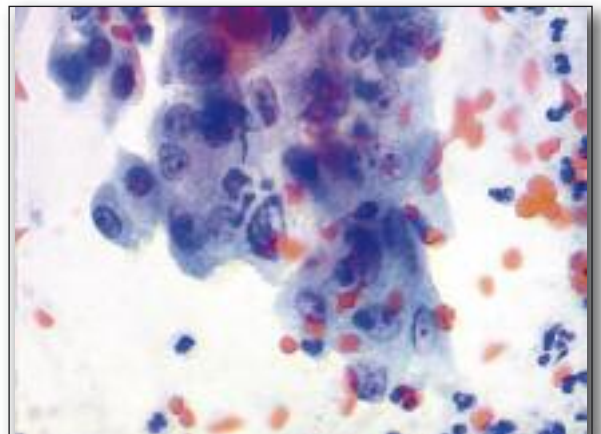
Case 4 x 40



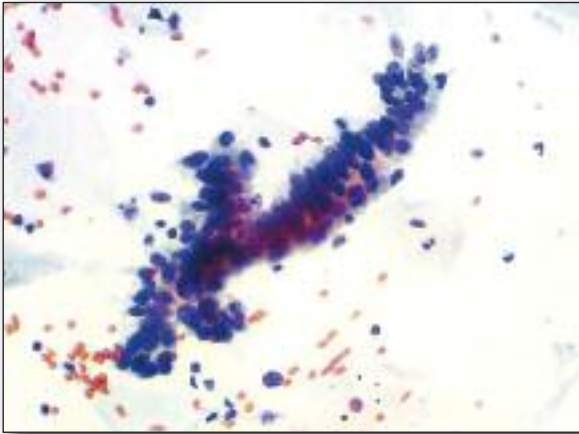
Case 4 x 40



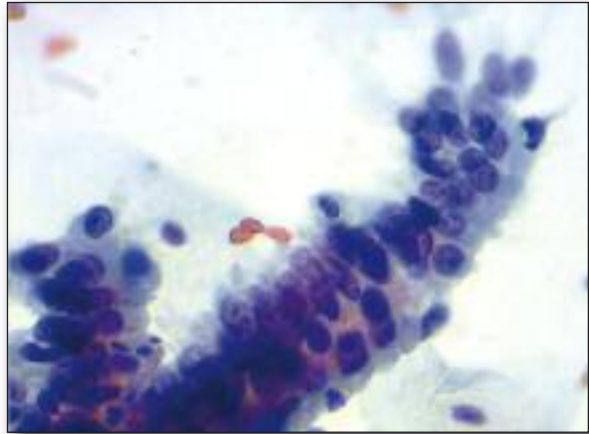
Case 5 x 20



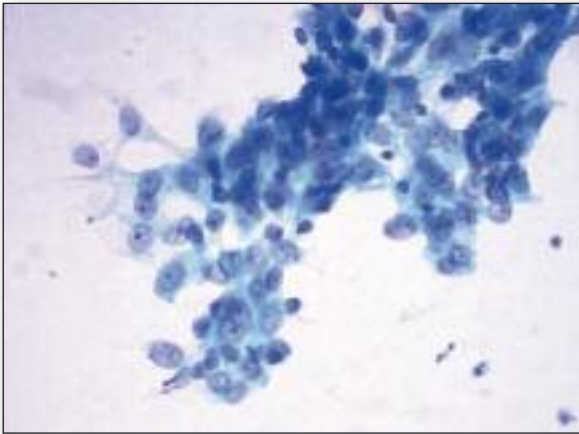
Case 5 x 40



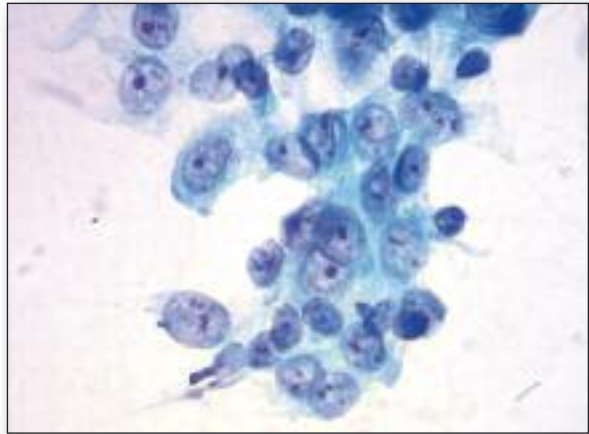
Case 6 x 20



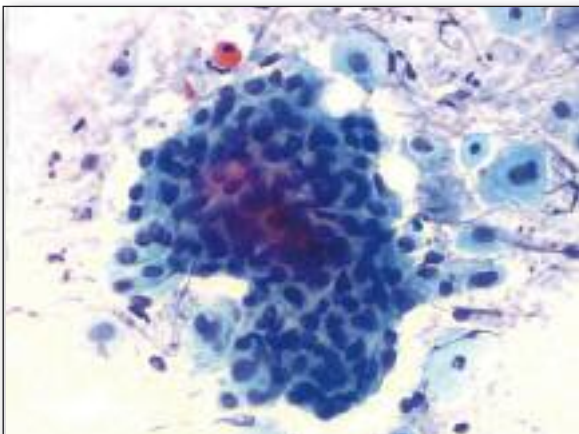
Case 6 x 40



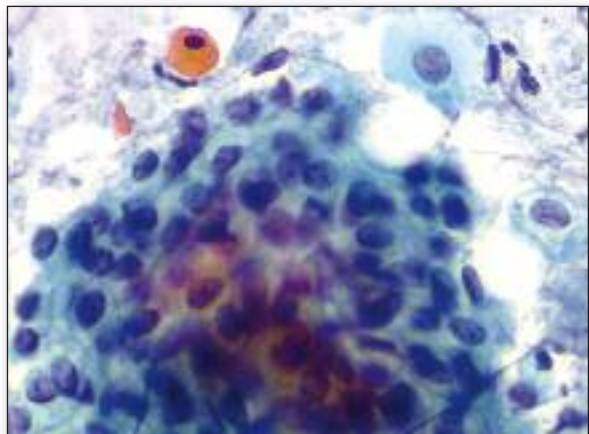
Case 7 x 20



Case 7 x 40



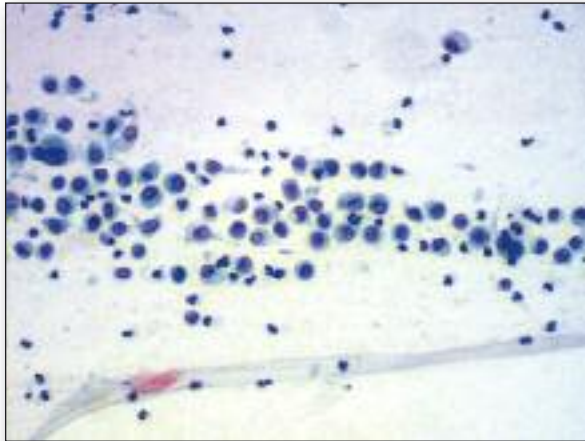
Case 8 x 20



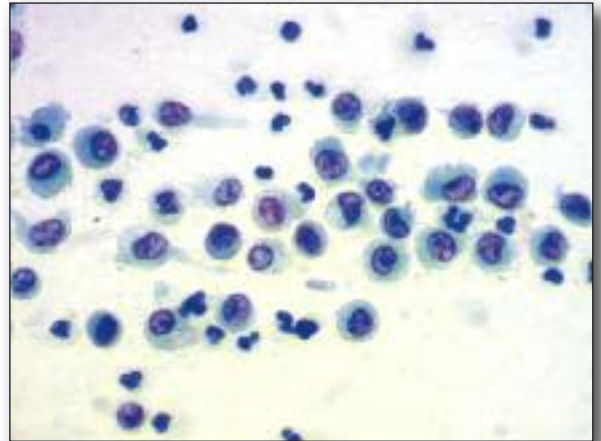
Case 8 x 40

Quiz continued overleaf

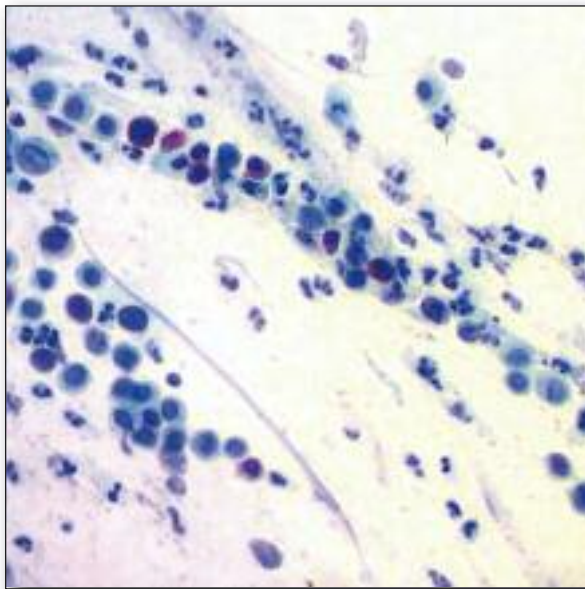
The following images are of single cells and bare nuclei. Both may look similar on low power, however after examining them on high magnification their differences may be identified in order to arrive at the correct diagnosis.



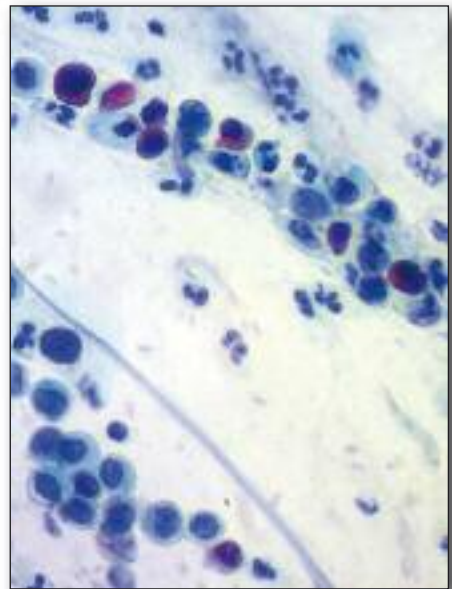
Case 9 x 20



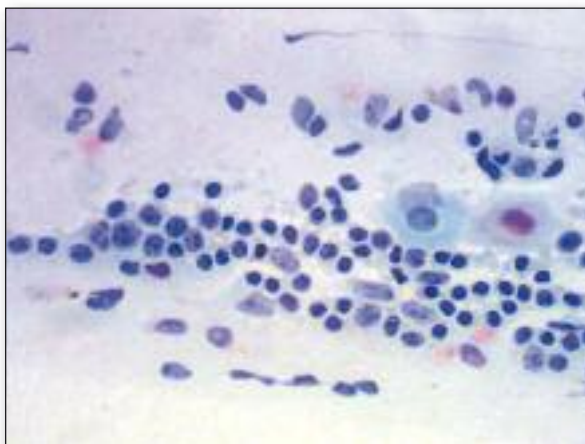
Case 9 x 40



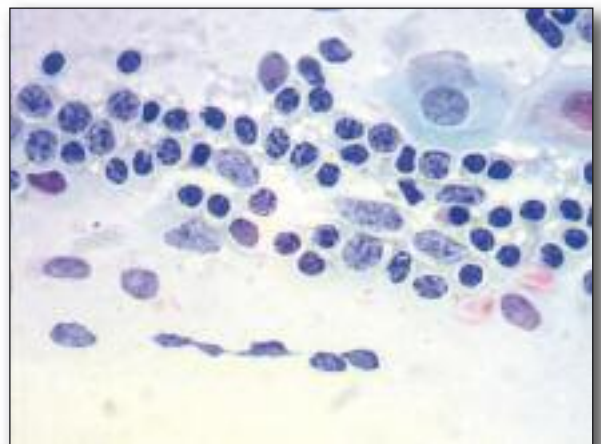
Case 10 x 20



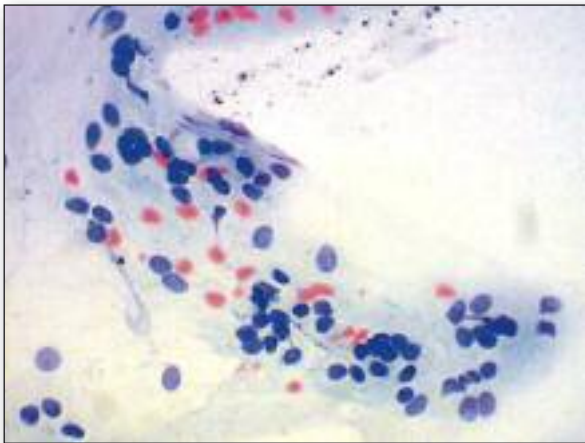
Case 10 x 40



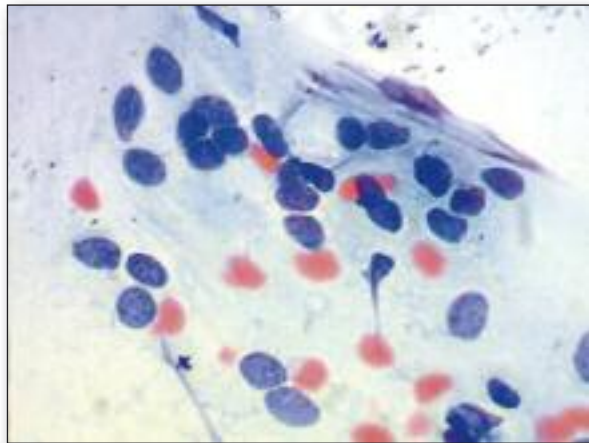
Case 11 x 20



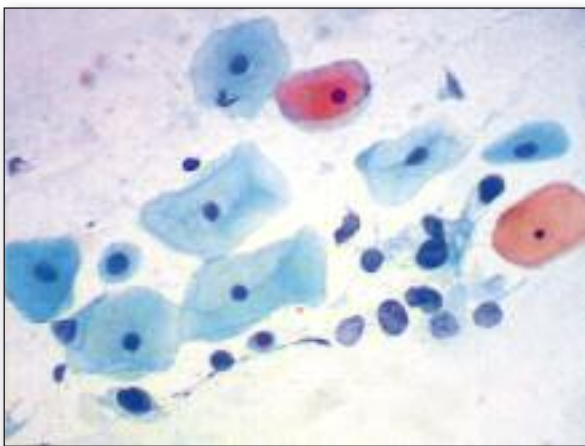
Case 11 x 40



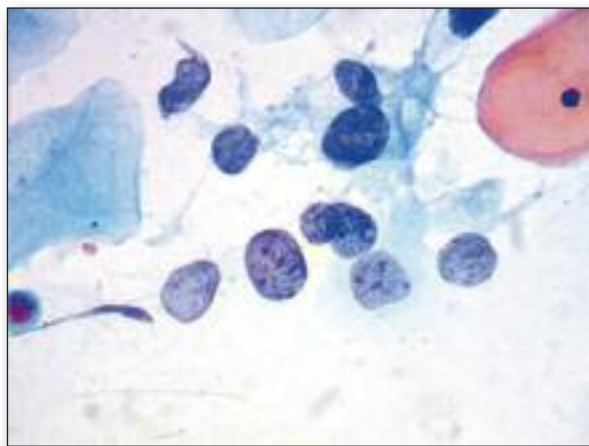
Case 12 x 20



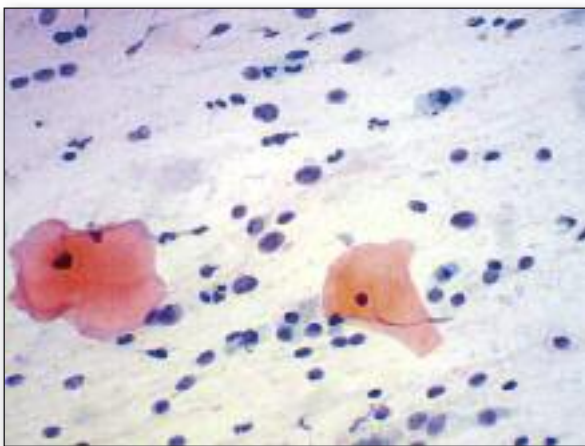
Case 12 x 40



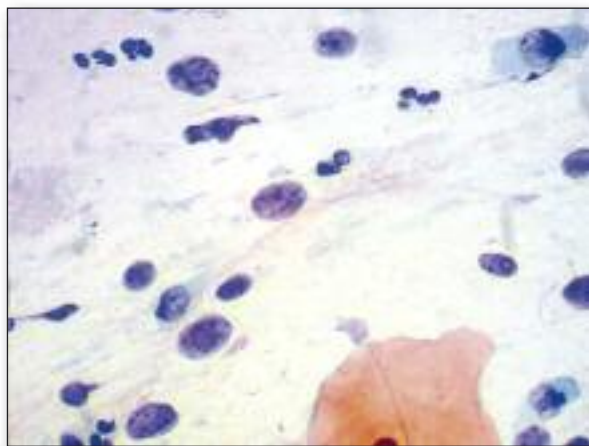
Case 13 x 20



Case 13 x 40



Case 14 x 20



Case 14 x 40

(Answers on page 36)

Case study answers (see pages 26–28)

Case Study One

Answer: Hodgkin lymphoma

The aspirate showed a mixed population of lymphoid cells with scattered plasma cells and lymphoglandular bodies in the background. Scattered Reed Sternberg and Hodgkin cells were seen with bilobed and polylobed nuclei with prominent nucleoli and moderate amounts of cytoplasm. No malignant epithelial cells were seen. A diagnosis of likely Hodgkin lymphoma was made and a formal lymph node biopsy advised to confirm the diagnosis and to subtype the lymphoma.

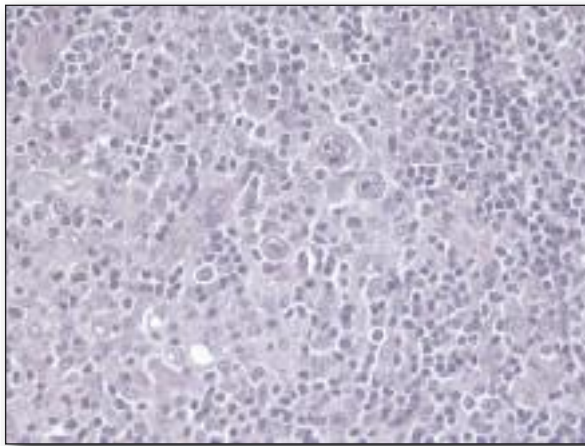


Image 1 Case study one

Subsequent histology showed classical Hodgkin lymphoma with the lymph node architecture partially effaced by an interfollicular infiltrate of Hodgkin and Reed-Sternberg cells, including mummified forms, amongst a background of macrophages, eosinophils, small

lymphocytes and a small number of plasma cells. The follicles present contained reactive appearing germinal centres. Focally, there was a suggestion of nodule formation with thickening of intra-nodal. Immunohistochemistry showed the Hodgkin/Reed-Sternberg cells to express CD30, CD15 and EBV-LMP1, but not CD20, CD79a, or EMA. Staining for CD2 and CD3 shows numerous reactive T-cells in the background.

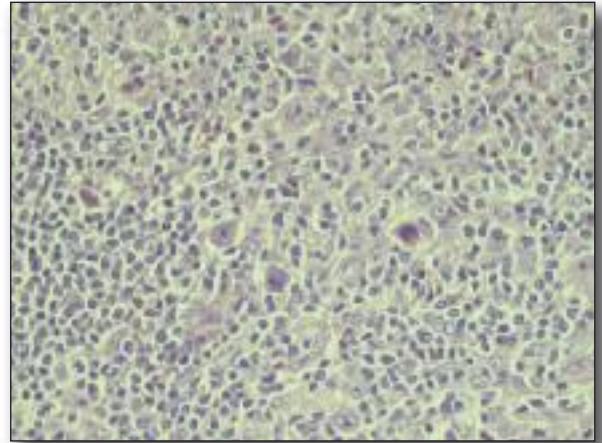


Image 2 Case study one

Pitfalls in the cytological diagnosis of Hodgkin disease include peripheral T-cell lymphoma and anaplastic large cell lymphomas which can contain large RS type cells. The other pitfall is an extensively sclerotic lymph node with Hodgkin lymphoma which does not yield atypical cells on FNA. It is always advisable to undertake formal lymph node biopsy when any lymphoma is suspected on cytology in order to confirm the diagnosis and accurately classify the malignancy.

Case Study Two

Answer: Metastatic amelanotic melanoma.

Examination of the aspirates showed similar features of mainly dissociated malignant cells with high nuclear cytoplasmic ratios, pleomorphic nuclei and coarse chromatin with small nucleoli. Occasional cytoplasmic vacuolations were identified. No intranuclear inclusions were seen and there was no pigment. All three aspirates were reported to the breast radiologist in the one-stop clinic as malignant, C5, in keeping with ductal carcinoma. Core biopsies taken at the same confirmed an invasive carcinoma, reported as grade 2 ductal carcinomas (below).

ER status and HER2 status was negative. The negative ER status was considered unusual by the reporting pathologist as the tumours were not thought to be high grade. The possibility that these multifocal carcinomas may represent metastatic disease was raised at the breast

cancer multidisciplinary team meeting. It was then disclosed that the patient had a malignant melanoma removed from her arm when she was seventeen.

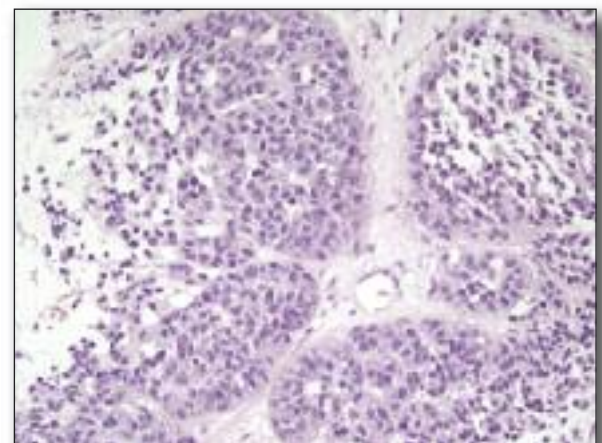


Image 1 Case Study Two

Subsequent immunocytochemistry revealed the tumour to be positive for S100, melan A (below) and HMB 45. The tumour was negative for CK, ER, HER2, BRST1 and CK 7 confirming malignant melanoma. Subsequent imaging of the axilla revealed enlarged nodes with malignant cells aspirated from one of the nodes. CT scan showed metastatic disease elsewhere.

A wide range of malignancies can metastasise to the breast, the most common being haematological malignancies, melanoma and carcinomas of lung, ovary, prostate, kidney and stomach. Neuroendocrine tumours from any site can also metastasise to breast. In clinical series metastases to breast represent about 0.2% to 1.3% of malignant tumours in the breast and is commoner in women. In about 30%, the breast lesion is the first sign of malignancy. There may be a long interval from the diagnosis of the primary to the appearance of a breast

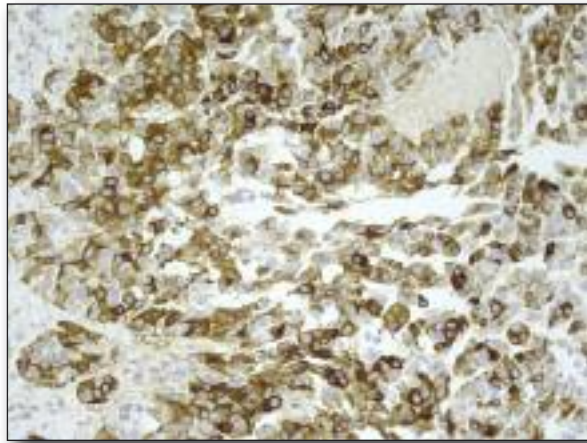


Image 2 Case study two

metastasis, especially with melanomas. History is therefore essential in reaching the correct diagnosis. The pathologist should always consider a metastasis if the morphology or immunostaining pattern is unusual.

Case Study Three

Answer: Pilomatrixoma.

Examination of the aspirate showed sheets of crowded epithelial cells with a heterogeneous population of dissociated cells in the background including some macrophages. No multinucleated cells were seen and there was no calcium. Occasional mitoses were present within the sheets. The background was dirty. The aspirate was reported as showing features suspicious of malignancy, C4.

The core biopsy showed fragmented sheets of crowded small atypical basophilic epithelial cells with scattered mitoses (the sheets being similar to those in the FNA)

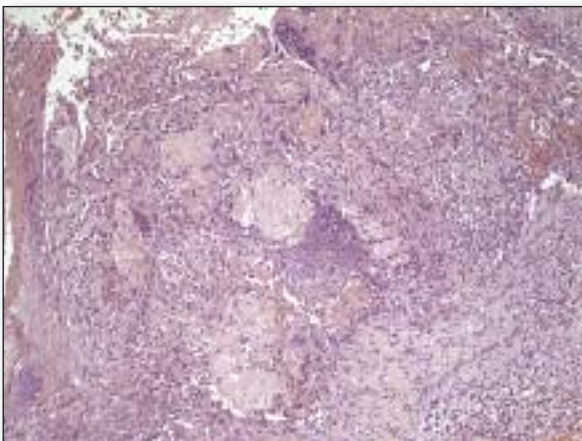


Image 1 Case study 3

together with sheets of eosinophilic shadow cells. The intervening connective tissue showed foreign body giant cells, a mixed inflammatory infiltrate with macrophages and calcium deposits. The histological appearances were considered to represent a pilomatrixoma (calcifying epithelioma of Malherbe), B2. After discussion at the breast cancer MDM it was agreed that the patient should have the lesion excised. The subsequent excision confirmed a small, excised pilomatrixoma. There was no evidence of malignancy.

Pilomatrixoma is a benign adnexal skin lesion, accounting for almost 20% of all pilar tumours and usually found in head, neck and upper extremities. They present as firm nodules, usually 0.5cm to 3.0 cm in diameter. They can be partly cystic and can contain bone. Surgical excision is the usual method of treatment. The appearances vary according to the age of the lesion with the lesions containing sheets of basophilic epithelial cells and sheets of eosinophilic shadow cells in varying quantities. The intervening connective tissue usually shows scattered foreign body giant cells, a mixed inflammatory infiltrate with macrophages, calcium deposits and bone fragments.

It should be remembered that primary skin lesions may occur in the skin of the breast and should be considered if the cytological appearances are unusual and do not fit the imaging or clinical picture, the 'triple approach'.

Quiz Answers

(see pages 29–33)

Case 1. HSIL

LP: Thickish sheet, loss of polarity, variation in size, shape nuclei

HP: variation in chromatin also appreciated.

Case 2. HSIL attached to sheet of normal endocervical cells

LP: 2 different patterns appreciated lack of polarity vs ordered arrangement

HP: variation in size, shape, chromatin. apoptotic debris.

Case 3. AIS

LP: disorganised glandular cells

HP: some crowding and pseudostratified, coarse chromatin.

Case 4. Transitional cell metaplasia.

LP: metaplastic-like cells, high N/C ratio.

HP: oval/spindle nuclei, a few showing longitudinal grooves.

Case 5. Reactive

LP: sheet disorganised metaplastic cells

HP: minimal crowding, flat sheet. fine chromatin, prominent nucleolus.

Case 6. AIS

LP: strip crowded, disorganised, glandular cells. Hint of feathering

HP: pseudostratified strip with coarse chromatin.

Case 7. Reactive

LP: flat sheet of slightly disorganised glandular-looking cells

HP: only slight variation in size, fine chromatin, prominent nucleolus.

Case 8. Atrophy

LP: disorganised group, some crowding

HP: cells same size and shape, fine chromatin, reasonable amount cytoplasm. Cell top right, with nucleus same size, shape, chromatin as in the group.

Case 9: histiocytes.

Case 10: severe dyskaryosis (CIN 3).

Case 11: lymphocytes.

Case 12: atrophic bare nuclei.

Case 13: atypical bare nuclei (associated with CIN 3).

Case 14: endocervical bare nuclei.

BAC to host EFCS 2016



SAVE THE DATE

2nd—5th October 2016

**Arena and Convention Centre
LIVERPOOL UK**

Check the website for more information
<http://www.britishcytology.org.uk/>



BAC British Association
for Cytopathology



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0114 226 8691

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Website: www.cytologytraining.co.uk

Administration:

Mrs K Hawke

0113 246 6330

Kathryn.hawke@nhs.net

One-Day Update Courses in ThinPrep® Cytology

A one course covering Aspects of Difficult Dyskaryosis for Experienced Staff

Will include bland Cell and Small Cell Dyskaryosis and
Reactive Changes versus Dyskaryosis

25th September 2014

Course Fee*: £95

Call Recall, Failsafe and the Impact of HPV testing and NHS re-organisation on the NHSCSP

A broad, one day course that should be of value to anyone
who is involved in Call Recall, the failsafe process and
anyone needing a broader understanding of these
functions within the NHSCSP. It would be of particular
value to those new to the screening programme and to
those involved in call / recall & failsafe who do not
normally have access to other forms of update training.

9th October 2014

Course Fee*: £95

HPV. Its role in cervical carcinogenesis and how to Detect it

A one day course that aims to give anyone involved in HPV
testing an overview of basic cell biology, the role that HPV
plays and the different techniques that can be used to
detect it.

19th March 2015

Course Fee*: £95

Update Courses in Non-Gynae Cytology

A series of three one day courses covering serous
fluids, urine & respiratory cytology and ideal for
anyone seeking an update in these areas, particularly
those intending sit the IBMS diploma. Also includes an
optional fourth half-day covering aspects of the IBMS
exam.

6th – 9th May 2015

Course Fee*: £95 / £230 / £345

One-Day Introductory Non-Gynaecological Cytology Workshops

Ideal for anyone requiring an introduction to non-
gynae cytology. These courses will cover specimen
preparation and understanding the morphology of
urine, respiratory and effusion cytology. Very useful
to anyone undertaking their Specialist Portfolio.

28th April – 1st May 2015

Course Fee*: £95 per day

One-Day Master-class in EBUS

Aimed at scientists and pathologists who are
embarking on starting an EBUS service with rapid on-
site assessment, or existing practitioners who wish to
update their knowledge. Course tutors are Dr
M.Wood, Consultant Respiratory Physician and Dr
B.Shambayati, Consultant Clinical Scientist who was
involved in setting up the on-site assessment process
in 2010

27th November 2014

Course Fee* : £120



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www.cytologytraining.co.uk

Administration:

Mrs K Hawke

0113 246 6330

Kathryn.hawke@nhs.net

Masterclass in Cytology

24–27 March 2015

Cervical Screening & HPV – 24 March

HPV. Its strengths and weaknesses, data on triage, test of cure and HPV primary screening from a UK sentinel site. The impact of vaccination & the future of cervical screening & the use of CINtec + as a molecular marker. False negative cytology with ThinPrep and SurePath samples identified through the NHSCSP invasive cancer audit

Respiratory Cytology – 25 March

Including exfoliative, TB/FNA and EBUS FNA cytology – preparation techniques, common pitfalls, and one year's experience of ROSE at EBUS clinics and the lessons learnt.

Thyroid and Soft Tissues – 26 March

Will include the appropriate diagnosis of follicular-patterned, cystic, papillary and oncocytic thyroid nodules by fine needle aspiration biopsy. Usefulness of TIRADS (thyroid image reporting and data system) and elastography with the use of TBSRTC compared with the RCPATH Thyroid Fine Needle Aspiration Diagnostic. Soft tissue will include the role of FNA and immunocytochemistry in the diagnosis of soft tissue tumours with a modern and practical approach and the indications for molecular testing in sarcomas.

Lymph Nodes and Salivary Glands – 27 March

How to deal with lymph node FNA – from clinic to molecular diagnostics. The workshop will include morphology, flow cytometry and molecular diagnostic aspects of lymph node cytopathology. FNA of salivary gland lesions session will cover how to deal with cystic salivary lesions, pigeonholing of salivary neoplasms, and pitfalls.

Faculty Includes:

Dr Sule Canberk, Istanbul, Turkey

Ms Nadira Narine, Manchester

Dr Tim Palmer Scotland

Dr Ashish Chandra, London

Dr Tanya Levine, London

Dr Durgesh Rana, Manchester

Mr Nick Dudding, Sheffield

Dr Mufaddal Moonim, London

Dr John H F Smith, Sheffield

Venue – East Pennine Cytology Training Centre. Leeds UK

Course fee: £380 full programme; £120 daily delegate rate

For further information and an application form: Please contact our Business Administration Team:

Kathryn.hawke@nhs.net or Tel: +44 113 246 6330

Director: Dr J H F Smith BSc MBBS FRCPath MIAC

BIRMINGHAM CYTOLOGY TRAINING CENTRE

All BCTC courses are provided in **SurePath and/or ThinPrep LBC**

IBMS RCPATH CPD accredited courses

INTRODUCTORY COURSES FOR CITY & GUILDS DIPLOMA IN CERVICAL CYTOLOGY

26 January - 6 February & 23 February - 6 March 2015; October 2015 (*dates tbc*)

This four-week course provides students with a theoretical and practical introduction to cervical cytology. A five-day Follow-on Course is offered free of charge to all those attending our Introductory Course.

FOLLOW-ON COURSES FOR CITY & GUILDS DIPLOMA IN CERVICAL CYTOLOGY

12-16 January 2015; 18-22 January 2016

The aims of this course are to revise the topics taught on the Introductory Course, consolidate skills and identify problem areas

PRE-EXAMINATION COURSES FOR THE CITY & GUILDS/NHSCSP DIPLOMA IN CERVICAL CYTOLOGY

19-21 January 2015; 25-27 August 2015

A three-day course for those preparing to take the City and Guilds/NHSCSP Diploma in Cervical Cytology

UPDATE COURSES IN GYNAECOLOGICAL CYTOLOGY (ThinPrep & SurePath)

2 October 2014 (Pitfalls in Glandular Reporting) 26 November 2014 (Borderline Changes—What now?)

6 January 2015 (*topic tbc*) 9 March 2015 (Checkers' Update)

27 April 2015 (*topic tbc*) 28 April 2015 (*topic tbc*)

NON-GYNAECOLOGICAL CYTOLOGY FOR TECHNICAL STAFF

23-24 April 2015

Ideal for those completing their portfolio for the Specialist Diploma

BIRMINGHAM HISTOPATHOLOGY COURSE

8-20 June 2015 (*provisional date*)

This two-week course provides topic based lectures on systemic pathology, slide review of selected cases followed by discussion and a revision session including mock exam in preparation for the FRCPath Part 2 exam.

HISTOPATHOLOGY MOCK EXAM COURSE

10-11 March 2015 (*provisional date*)

The Mock FRCPath Part 2 Exam Course is designed to familiarise trainees with the format of the exam, style of questions & timings and provides guidance on how to approach the exam.

GYNAECOLOGICAL CYTOLOGY FOR TRAINEE PATHOLOGISTS (StRS)

16-17 February 2015; 3-4 September 2015

The programme for this course is a combination of lectures workshops and multiheader sessions. This course includes a mock exam and is particularly suitable as revision for the FRCPath Part 2 exam

NON-GYNAECOLOGICAL CYTOLOGY FOR TRAINEE PATHOLOGISTS (StRS)

10-14 February 2015; 8-12 September 2015 (*courses include optional Saturday am for personal revision*)

The programme for this course is comprehensive and includes the salient aspects of diagnostic non-gynaecological cytology. This course includes a mock exam and is particularly suitable as revision for the FRCPath Part 2 exam

WEST MIDLANDS AUTOPSY PATHOLOGY COURSE

14-15 September 2015

For trainees in preparation for the Autopsy element of the FRCPath exam and Consultant Pathologists involved in coronial / procurator fiscal work as an update for annual appraisal and revalidation.

INTRODUCTORY COURSE FOR ST1s

30 November—4 December 2015 (*provisional date*)

Gynaecological and Non-Gynaecological Cytology including Autopsy element

LBC Conversion Courses, Ad hoc workshops and Off Site workshops can be arranged on request—please contact BCTC

Please see our website for full list of our courses. For further details and reservations please contact Louise Bradley or Amanda Lugg
Birmingham Cytology Training Centre, Birmingham Women's Hospital, Birmingham, B15 2TG, Phone: 0121 627 2721, Fax: 0121 627 2624,
Email: Louise.Bradley@bwnft.nhs.uk or Amanda.Lugg@bwnft.nhs.uk Website: <http://www.bwhct.nhs.uk/cytology-training-centre>



2015 COURSES

All course information and online booking form can be found on our website
www.lrctc.org.uk

Pre-Registration Gynaecological Courses

INTRODUCTORY COURSE IN GYNAECOLOGICAL CYTOLOGY (Thinprep®)

- 2nd – 27th February
- 5th – 30th October

Course fee:

- Contracted London regional students: No charge
- All other students: £1100

FOLLOW UP COURSE (Thinprep®)

- 13th April – 17th April
- 27th – 31st July

Course fee:

- Those who attended the Introductory Course at LRCTC: No charge
- Other participants: £400

PRE – EXAM COURSE (Thinprep®)

- 5th – 9th January
- 21st – 25th September

Course fee:

- Contracted London regional students: Free
- Non-Contracted students: £400

Medical Practitioners Courses

PATHOLOGISTS COURSE – GYNAE

This two day course covers gynaecological cytology.

- 4th – 5th + 6th (Optional Mock Exam) **March**

Course fee: - £200 Mock exam - +£50

PATHOLOGISTS COURSE – NON GYNAE

This four day course covers non-gynaecological cytology.

- 9th – 12th + 13th (Optional Mock Exam) **March**
- 14th – 17th + 18th (Optional Mock Exam) **September**

Course fee: - £ 400 Mock exam - +£50

Please indicate on the online booking form if you wish to attend the mock exam.

MEDIC'S 1-DAY UPDATE COURSE

A refresher course for consultant pathologists/AP's

- 22nd May
- 30th September

Course fee:

- Contracted London regional participants: Free
- Non-Contracted participants: £150

Post Registration Courses

BMS/CYTOSCREENER UPDATE COURSE

- 13th – 15th January
- 17th – 19th March
- 22nd – 24th April
- 19th – 21st May
- 8th – 10th June
- 2nd – 4th September
- 24th – 26th November
- 9th – 11th December

Course fee:

- Contracted London regional participants: Free
- Non-Contracted participants: £350

Introductory Non-Gynae Courses

RESPIRATORY CYTOLOGY COURSE

- 15th – 16th June

SEROUS FLUID CYTOLOGY COURSE

- 10th – 11th September

URINE CYTOLOGY COURSE

- 2nd – 3rd December

Course Fees:

- Contracted London regional participants: Free
- Non-Contracted participants: £200

Medical Laboratory Aides (MLA's) Courses

INTRODUCTORY MLA COURSE

This is an Introductory course designed to cover topics such as overview of the NHSCSP, terminology, role of an MLA and audit.

- 27th April
- 18th November

Course Fee:

- Contracted London regional participants: Free
- Non-Contracted participants: £150

Book online at www.lrctc.org.uk

All courses above are CME, IBMS CPD and NAC CEG accredited.

Further details/information can be obtained by contacting 0208 669 5270 or emailing nwlh-tr.lrctcbooking@nhs.net or by visiting our website.



Directorate of Laboratory Medicine

Central Manchester University Hospitals **NHS**

NHS Foundation Trust

THE NORTH WEST CYTOLOGY TRAINING CENTRE COURSES 2014/15

Bespoke training possible on request

Please contact the Centre with your requirements



Non Gynae Master Class for Medical Staff

EBUS (6 RCPATH CPD credits)

11th November 2014

Course fee: £150 / £120 for NW regional staff

LBC Update Course in Gynae Cytology for BMSs/Cytoscreeners (SurePath)
*£100 per day

Topic A – Borderline

Topic B – Atrophy

Topic C – Pitfalls and lookalikes

29th Sept, 15th Dec 2014 (Topic C),

30th Sept, 17th Dec 2014 (Topic B),

1st Oct, 16th Dec 2014 (Topic A)

Next round of updates to start
March 2015

Pre-Examination Course for the C&G Diploma in Cervical Cytology (Surepath)*

Bespoke training on request

FRCPath COURSES 2014/15

Non Gynaecological Cytology Revision Course

August 18th – 22nd 2014

February 2015 (TBA)

FRCPath Pre – Exam course

September 15th – 19th

March 2015 (TBA)

20% discount for regional trainees

Gynae Master Classes*

Courses aimed at tackling difficult areas, for Medical and BMS Consultant staff, and experienced staff wishing to challenge their knowledge

Please check website for new topics and dates

Novice Sample Taker Training

Course fee £330

Further dates to be announced

Primary Care ½ day Update Event

11th September 2014

17th October 2014

18th November 2014

4th December 2014

Fee £30

Introductory Course for NHSCSP Diploma in Cervical Cytology*

(subject to demand)

20th July – 14th August 2015

Fee £1000

*Mandatory Courses Are Free Of Charge to North West Region Technical Staff.

Please note that all gynae courses are based on Surepath morphology

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Scottish Cytology Training School

Programme 2014/15

No course fee is charged for Gynae cytology courses to employees of Scottish NHS Trusts

Training School Director

Dr Edward Duvall

Tel: 0131 242 27123

Email: Edward.Duvall@luht.scot.nhs.uk

Training School Manager

Sue Mehew

Tel: 0131 242 7149

Email: Sue.mehew@luht.scot.nhs.uk

Training School Administrator

Mrs Linda A Cooper

Training School Administrator

Pathology Department

Royal Infirmary of Edinburgh

51 Little France Crescent

Edinburgh

E116 4SA

(Available: 0800 – 1515, Tues - Thurs)

Tel: 0131 242 7135

Fax: 0131 242 7169

Email: Linda.Cooper@luht.scot.nhs.uk

**Application forms available on
request from:**

scis@nhslothian.scot.nhs.uk

NIHSCSP Accredited Training Centre

Courses held at Royal Infirmary of Edinburgh unless states (SGH) Southern General Hospital Glasgow.



Introductory Course

23rd February – 22nd March 2015

£1000

Introductory Course Part 2 tbc

10th November – 14th November 2014

Update Course

4th – 5th November 2014 (SGH)

3rd – 4th December 2014

3rd – 4th February 2015

£100 per day

Pre-Exam Course

19th – 21st Aug 2014 (for Oct Exam)

£250

Workshops

21st Nov 2014 – Medical Staff

£100

Non-Gynae Course for Trainee Medical (ST3) & BMS staff

23rd – 26th September 2014

£100 per day

Course for Colposcopists

January 2015 tbc

*Non-NHS Labs – price on application
All courses are in Liquid Based Cytology (Thin Prep)
Courses are CPD accredited*

SOUTH WEST REGIONAL



2015 Course Schedule

Date	Gynae Courses	Fee*
2-27 March 21 Sept-16 October	Introductory in Gynae Cytology	NHS £1000 Other £1200
23-25 February 19-21 May 15-17 September 1-3 December	Update in Cervical Cytology for Technical Staff	NHS £300 Other £350
29 April 8 December	Update for Cytology Checkers	£100
22 April 11 November	Update in Cervical Cytology for Pathologists & Consultant BMS's & Holders of the Advanced Specialist Diploma in Cervical Cytology	£100
10 June	Gynae Histology for Technical Staff	£100
3-4 November	Gynae Pathology for Trainee Colposcopists	£200
26-27 January 11-12 May 7-8 September	Cervical Sample Taker Training	£250
14 May 18 November	½ Day Update in Cervical Screening for Sample Takers	

Date	Non-Gynae Courses	Fee*
10 February	Serous Fluid Cytology	£100
15 April	Respiratory Cytology	£100
20 October	FNA Cytology	£100
24 November	Urinary Tract Cytology	£100
2-5 February 6-9 July	Non-Gynae for Trainee Pathologists	£400

**PLEASE NOTE THAT NO FEE IS APPLICABLE FOR NHS STAFF BASED IN THE SOUTH WEST REGION*

South West Regional Cytology Training Centre

Department of Cellular Pathology
Lime Walk Building
Southmead Hospital
Bristol BS10 5NB

Tel: 0117 323 5649
Fax: 0117 323 5640
Email: SWRCTC@nbt.nhs.uk

www.cytology-training.co.uk

The BAC are pleased to announce further details of the

**2014 Scientific Conference, AGM and Trade Exhibition
9 – 11th October 2014
Crowne Plaza hotel, Birmingham city centre**

Suitable for Pathologists, Biomedical Scientists and Cytoscreeners of all levels of experience, the scientific programme will provide a mix of both gynaecological and diagnostic cytology, with topics including:

Various aspects of HPV	Anal screening
Use of P16	Lymph node
Small cell ca of cervix	Respiratory / molecular
Medico-legal issues	BMS histopathology reporting

**Confirmed overseas speakers include Professor Marshall Austin (USA)
and Dr Christine Bergeron (France)**

The Erica Wachtel memorial lecture will be delivered by Dr Christine Waddell

Proffered papers and posters are requested and there will be a cash prize for the best overall presentation — see the BAC website for full details. All proffered paper and poster presenters will receive a voucher off the registration fee for a future BAC scientific meeting, funded by the BAC educational bursary fund.

The social programme will commence on the evening of Thursday 9th October with a drinks and canapé reception for the opening of the Trade Exhibition by Mr Nick Kirk, President of the IBMS.

The conference dinner at the Crowne Plaza on Friday 10th October will be followed by after dinner entertainment and a disco.

Registration fees have been held at very competitive rates for both the full package and day delegate rates. The full package does not include accommodation but this is available at the Crowne Plaza or one of the many other nearby city centre hotels.

For the full programme and booking details please see the BAC website <http://www.britishcytology.org.uk>

A discount for early booking applies until April 30th so don't delay and register today!

STOP PRESS

The BAC are delighted to announce that they will be hosting the participant feedback sessions for both the non-gynae EQA and the non-gynae technical EQA schemes on the afternoon of Thursday 9th October at the Crowne Plaza, prior to the conference. Details of both meetings will be circulated by the respective scheme organisers. Delegates attending either of these meetings will be welcome to register for the conference.

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Material for publication should be sent direct to the Editor; all other correspondence with the Association should be addressed to the Secretary.

Front Cover image: The editor is indebted to Mrs Jenny Davies CSci FIBMS CMIAC, Northwest Cytology Training Centre Manager for the pine pollen (botanically identified) on a SurePath sample (polymorph out of focus gives size).

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