Best Practice No 170

Investigation of infertility with the emphasis on laboratory testing and with reference to radiological imaging

C Williams, T Giannopoulos, E A Sherriff

This review will discuss the investigation of infertility, with emphasis on laboratory testing and reference to the value of other investigations, including clinical and radiological. The role of laboratory investigations is viewed within an appropriate clinically directed pathway that includes medical, surgical, and social history together with environmental factors. Because embryology and assisted reproduction techniques are developing rapidly and produce continuous changes in everyday practice, this article gives a critical review of the plethora of tests that are currently used.

DEFINITION OF SUBFERTILITY

The definition of infertility varies considerably, particularly in relation to the length of time of regular unprotected intercourse. Most practitioners would start investigations if the woman does not conceive after a period of one year. However, individual circumstances will differ and couples should generally be seen whenever they think there is a problem. Often, there are other factors such as the woman’s age (usually more than 37 years), previous surgery, or irregular menstrual cycles that warrant earlier investigation than the usual one year of trying.

ANALYTICAL ISSUES

Laboratories must ensure that reference ranges, conditions of collection, and specimen preservation are appropriate to their clinical applications. Clinicians may need advice upon the reproducibility of assays and the transferability of assay data from the literature to other sites. Although three luteinising hormone (LH)/follicle stimulating hormone (FSH) assays account for over 70% of the UK market there are many more in use. Most of the 10 most popular LH and FSH assays in the UK have a geometric coefficient of variation of 10% or less tested within the ovulatory range, but some are systematically better than others. Some LH assays crossreact with human chorionic gonadotrophin, which may be clinically important in the investigation of the amenorrhoeic patient. The coefficient of variation (CV) profile of most oestradiol assays is not suited to discriminating low values, with at best an interlaboratory CV of 25% at 200 mU/litre, increasing exponentially below this value. Clinical samples should be referred to specialist laboratories when precise measurement is required at lower values.

“...In combined data from over 5000 infertile couples, 30% of problems related to ovulation and 22% to seminal defects...”

Macroprolactinaemia, as a high molecular weight complex of prolactin (PRL), reacts to a variable extent in commercial PRL kit immunnoassays, resulting in raised PRL values. Macroprolactin was found to be mainly responsible for raised “prolactin” in one out of four to five sera where values were up to two to three times higher than the top of the reference range; these observations call into question the derivation of reference ranges themselves. Allowing for their

ROLES AND LIMITATIONS OF THE LABORATORY

In developed countries, 22% of infertility is caused by a male factor alone and in a further 21% both male and female factors are involved. In combined data from over 5000 infertile couples, 30% of problems related to ovulation and 22% to seminal defects. Laboratories potentially contribute to the diagnosis of over 50% of couples investigated.

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Abbreviations: ASAB, antisperm antibody; BMI, body mass index; CMSFP, cervical mucous sperm penetration testing; CV, coefficient of variation; DHEAS, dehydroepiandrosterone sulfate; EQA, external quality assessment; FSH, follicle stimulating hormone; IAT, immunobead testing; ICSI, intracytoplasmic sperm injection; LH, luteinising hormone; MAR, mixed antiglobulin reaction; PCOS, polycystic ovarian syndrome; PRL, prolactin; SHBG, steroid hormone binding globulin; TFF, thyroid function test; WHO, World Health Organisation

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lower relative proportions, higher ranges of raised PRL may be equally affected by macroprolactin and there are not enough data to be confident about defining a value at which macroprolactin can be neglected as a possible cause of raised PRL, although evidence indicates that macroprolactin is rarely reported at total PRL > 20 000 mU/litre (Dr M Fahie-Wilson, personal communication, 2002). It has been recommended that when total PRL > 700 mU/litre the sample should be investigated for the presence of macroprolactin, and measurement of PRL after treatment with polyethylene glycol, which precipitates macroprolactin, is one way of doing this. Because at this stage the clinical consequences of this entity seem relatively benign, referral and intensive investigation of affected patients may not be necessary; however, follow up of a large cohort in terms of longterm clinical outlook is required (Dr M Fahie-Wilson, personal communication, 2002). Because macroprolactinaemia does not exclude a pituitary adenoma, perhaps pituitary imaging studies should be ordered in patients with macroprolactinaemia when this is indicated by clinically relevant features.

PRL is susceptible to stress effects and a protocol should be in place to identify this. A small study and other evidence suggest that venepuncture does not raise PRL and serial testing at 0, 30, and 60 minutes was reported to identify and exclude stress related hyperprolactinaemia. PRL stimulation tests and the nocturnal profiling of prolactin probably add little to the differentiation of adenosas from other causes of increased PRL. LH measurement may exceptionally be affected by a very rare LH β-subunit variant reducing LH detection.

Analytical services for sperm have been relatively inconsistent in term of the quality of performance in external quality assurance (EQA) programmes and the elements of service provided, but are improving (Dr AD Atkinson, personal communication, 2002). The UK External Quality Assurance Scheme data now indicate that most non-specialist laboratories perform satisfactorily (Dr AD Atkinson, personal communication, 2002).

LIMITS UPON DIRECT INTERPRETATION OF TEST RESULTS

Significantly abnormal test results do not necessarily preclude successful reproductive function. For instance, fertile and infertile men are not separated by World Health Organisation (WHO) criteria because pregnancy may occur as long as motile sperm are evident. Some identifiable defect or functional failing relating to sperm occurs in 20% to 30% of couples investigated for infertility subject to the criteria used and studies undertaken. Although abnormal semen analysis parameters such as count and percentage of normal forms are reliable indicators of subfertility, some tests such as sperm antibody assays are not.

SALIVA AND STEROID INVESTIGATIONS

Clinicians may not be aware that clinical sampling using saliva for steroid measurements is practicable in some circumstances, including the measurement of oral progesterone. In general, however, significant interindividual differences occur in saliva to serum ratios and these have not been investigated under the range of physiological and therapeutic conditions that may disturb them. Few papers share identical methods and it can be assumed that transferability of absolute reported values will be limited. Saliva matrix effects vary significantly between different manufacturers’ radioimmunoassay kits and systematic differences were evident between nine laboratories measuring saliva testosterone in an EQA survey. Salivary assays should only be considered where relevant analytical and interpretive expertise permits.

THE INVESTIGATION OF THE INFERTILE COUPLE

There is no evidence that the recommended practice of managing the male and female partner together, as opposed to separately, improves either reproductive outcomes or non-reproductive outcomes, such as acceptance of infertility, or that temperature charts and LH detection methods to time intercourse improve outcome.  

INVESTIGATIONS OF THE FEMALE PARTNER

Serum progesterone: use as a key test

Recurring menstrual cycles are usually (95% confidence) ovulatory if they vary by no more than a few days within normal confidence limits of duration and are associated with premenstrual symptoms. However, ovulation should still be confirmed by the measurement of serum progesterone in the midluteal phase.

A value of serum progesterone of > 30 nmol/litre is considered proof of adequate ovulation, although the WHO uses 18 nmol/litre to confirm ovulation (appendix 1). Progesterone values have either been measured in women with regular menstrual cycles that are assumed to be ovulatory or in conception cycles where ovulation must have taken place.

It is important that the sample is timed in relation to the subsequent onset of menses, otherwise interpretation is difficult. A mistimed sample is the most common cause of an abnormal result. The sample should be taken seven days before the expected onset of menses. If a woman has a long or unpredictable cycle the sample may need to be repeated weekly until the next menstrual cycle starts.

Serum prolactin, FSH, LH, thyroid tests, and oestradiol in the broad classification of disorders

Anovulatory infertility is the most common cause of female infertility, often characterised by irregular menstruation, amenorrhoea, or oligomenorrhoea; however, ovulatory dysfunction may occur coincidentally with apparently regular cycles. Performance of these tests, usually done on day 2–4 of the cycle (if there is one), in concert with clinical observations, will normally identify the four main causes of ovulatory failure, namely: normogonadotrophic anovulation, hyperprolactinaemia, hypogonadotrophic hypogonadism, and hypergonadotrophic hypogonadism. In the absence of periods, greatly raised FSH (> 50 IU/ml) is diagnostic of ovarian failure; however, most patients with oligomenorrhoea or amenorrhoea will have normal gonadotrophins as part of the polycystic ovarian syndrome (PCOS). When serum oestrogen is normal, the maximum normal prolactin should be in the range 600–800 mU/litre. Raised prolactin may be physiological (such as, pregnancy) or may indicate pituitary prolactinoma, stalk compression by hypothyamic or pituitary tumours, thyroid failure, PCOS, psychotherapeutic medication, or other pathology (table 1).

Anovulatory infertility is the most common cause of female infertility, often characterised by irregular menstruation, amenorrhoea, or oligomenorrhoea.

Table 1 Causes of hyperprolactinaemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td>Pregnancy, stress, nipple stimulation, coitus</td>
</tr>
<tr>
<td>Pituitary prolactinoma</td>
<td>Any pituitary/hypothalamic tumour that compresses the pituitary stalk</td>
</tr>
<tr>
<td>Idiopathic hypersecretion</td>
<td>Primary hypothyroidism</td>
</tr>
<tr>
<td>Pharmacological causes</td>
<td>Phenothiazines, butyrophenones, pimozide, cimetidine, methyldopa</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome</td>
<td>Renal/liver failure</td>
</tr>
<tr>
<td>Traumatic or neoplastic lesions of the thorax or spine</td>
<td>Ectopic production of prolactin by extrapituitary tumour</td>
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"Anovulatory infertility is the most common cause of female infertility, often characterised by irregular menstruation, amenorrhoea, or oligomenorrhoea."
Low LH and FSH concentrations (< 5 mIU/ml), low oestradiol values (< 40 pg/ml), along with a negative gestagen challenge test (no withdrawal bleeding) result from hypogonadotropic hypogonadism, which is usually a result of primary hypothalamic or pituitary failure. Other causes include excessive stress or exercise, malnutrition, or low weight. Assessment of anterior pituitary function reserve should be undertaken in accordance with local protocols. The precise measurement of low oestradiol concentrations can also be useful in the investigation of precocious puberty and Turner’s syndrome.

Currently, the FSH concentration is the favoured marker for assessing ovarian reserve and for predicting the response to superovulation, with a good correlation with pregnancy rates. FSH values are checked on day 2 to day 4 with a cutoff point of 12 IU/litre. Once the FSH concentrations start to fluctuate, there is already a decreased ovarian reserve and it is not clear whether starting stimulation in a later month with “normal” FSH values will give a better result.

Hypergonadotropic hypogonadism is defined by raised FSH concentrations (> 20 mIU/ml) and indicates ovarian failure. In younger women the cause may be idiopathic, iatrogenic, or genetic (for example, Turner’s syndrome). In older women near the end of their reproductive life, a raised FSH concentration is the result of aging of the ovary and therefore indicates imminent menopause. Patients younger than 30 years of age should have a karyotype determination because the incidence of chromosomal abnormalities in this age group peaks in the early 40s. Patients younger than 30 years of age should have a karyotype determination because the incidence of chromosomal abnormalities in this age group peaks in the early 40s.

The Royal College of Obstetricians and Gynaecologists recommends that thyroid function tests (TFTs) should be reserved for the particular subset of infertile women with irregular menstrual cycles and for women with signs and/or symptoms of thyroid disease, and PRL measurement for those women with amenorrhoea, oligomenorrhoea, or clinical symptoms of hyperprolactinaemia, such as galactorrhoea. If women with amenorrhoea, oligomenorrhoea, or clinical irregular menstrual cycles and for women with signs and/or symptoms of thyroid disease, and PRL measurement for those women with amenorrhoea, oligomenorrhoea, or clinical symptoms of hyperprolactinaemia, such as galactorrhoea. If patients younger than 30 years of age should have a karyotype determination because the incidence of chromosomal abnormalities in this age group peaks in the early 40s.
Endometrial biopsy
As a way of evaluating the luteal phase, endometrial biopsy is not of confirmed value as a routine investigation.

Hysterosalpingogram, laparoscopy, and hysterosalpingo contrast
Hysterosalpingography (HSG) and laparoscopy with chromopertubation are not mutually exclusive because apart from testing tubal patency they provide different information. The procedure of choice is determined by the clinical circumstances of both partners. Hysterosalpingography gives information about the uterine cavity that a laparoscopy and dye test cannot provide (unless combined with hysteroscopy), whereas laparoscopy gives information about the rest of the pelvis, including peritubal adhesions, endometriosis, and ovarian pathology. Laparoscopy has a 1–2% complication rate and a mortality rate of eight in 100 000. A hysterosalphingogram may be used as a screening test for tubal patency in low risk couples. However, when an evaluation of the pelvis is required a diagnostic laparoscopy with dye transit is the procedure of choice. Those with risk factors for pelvic or tubal disease or an abnormal pelvic examination should proceed directly to laparoscopy because they are more likely to have pelvic pathology. Hysterosalpingo contrast sonography is increasingly used as a test for tubal patency.

INVESTIGATIONS OF THE MALE PARTNER
Male parenting cannot be taken as evidence of sperm quality. Subject to socioeconomic, regional, and international weighting factors, 1% to 30% of children cannot be genetically matched to their presumptive fathers. Although reliable authenticated data on non-paternity rates are sparse it seems probable that the UK rate lies close to 1%.

Semen analysis
Evaluation of sperm morphology continues to cause problems for many people, reflecting internal and external quality assurance and training issues under active consideration (Dr AD Atkinson, personal communication). Laboratories should perform semen analysis according to recognised World Health Organisation methodology and subscribe to the appropriate external quality assurance scheme.

Table 2 Suggested protocols for semen collection and World Health Organisation (WHO) normal values

<table>
<thead>
<tr>
<th>Collection of a semen sample</th>
<th>WHO values for “normal” semen analysis include</th>
</tr>
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<tbody>
<tr>
<td>Abstain for two to three days</td>
<td>Volume 2 ml or more</td>
</tr>
<tr>
<td>Produce the sample by masturbation, not by coitus interruptus</td>
<td>Concentration, 20 million/ml or more</td>
</tr>
<tr>
<td>Do not use condoms for collection of the sample or lubricant jellies</td>
<td>Matility, 50% progressive motility or more</td>
</tr>
<tr>
<td>Use a wide mouth sterile plastic specimen pot to collect the sample</td>
<td>Morphology, 15% or more normal forms</td>
</tr>
<tr>
<td>Mark the container clearly with the name, date and time of production, and the date of the immediate preceding ejaculation by coitus or masturbation</td>
<td>White blood cells, &lt;1 million/ml</td>
</tr>
</tbody>
</table>

No of these tests has been shown to perform well in isolation. However, it is possible that a combination of these tests may be better at predicting fertilisation. The advent of intracytoplasmic sperm injection (ICSI), which overcomes defects in fertilising ability, may have made such tests less relevant to eventual pregnancy outcome.

Computer assisted seminal analysis (CASA)
The software in use measures the amplitude, frequency, and velocity of spermatozoa, but as yet has no confirmed value in predicting fertilisation potential and is subject to sampling variation.

Hypo-osmotic swelling assay
This tests the functional integrity of the plasma membrane of the spermatozoa by observing curling of the tail under hypo-osmotic conditions. Neither alone or in combination with traditional semen characteristics has it proved to be of value in predicting pregnancy outcome.

Sperm penetration tests
There is wide disagreement about the outcome of cervical mucous sperm penetration testing (CMSPT) and its association with fertilisation potential. In an attempt to overcome some of the difficulties with in vivo testing, as typified by postcoital tests and CMSPT, attempts have been made to replace human ovulatory cervical mucous with hyaluronic acid polymers or bovine cervical mucous. However, these tests only seem to reflect sperm motility and do not give added information about fertilisation potential.

Hemizona assay
The ability of spermatozoa to bind to the zona pellucida may be tested in ova stored in a high salt solution. Because zona binding is dependent on oocyte maturity, the oocyte is divided in half with a micropipette so that each half acts as its own control with a fertile sample. This test does have some correlation with fertilising potential but false positive hemizona
assay results can occur because the fertilisation defect may be in functional steps beyond the tight binding of the sperm to the zona pellucida.

Hamster oocyte penetration assay
There is a lack of standardisation in this laboratory technique. Longterm follow up (up to 68 months) of couples who have had a hamster egg penetration assay performed has shown no significant difference in the rate or incidence of pregnancy in relation to the results of this test, as analysed by life table analysis. Most studies have been difficult to interpret because of the lack of consensus arising from quality assurance issues.

Biochemical aspects of sperm function
Acrosin is one of the enzymes present in the acrosome. Its activity has been reported to be greater in fertile than in infertile males; however, there are no prospective evaluations correlating acrosin activity with fertilisation rates in patients undergoing assisted reproduction techniques. The measurement of the production of reactive oxygen species released by spermatozoa may be used as an indicator of sperm function, but at present this is still a research tool. None of these tests has been shown to perform well in isolation. It is possible, however, that a combination of these tests may be better at predicting fertilisation, although the advent of ICSI, which overcomes defects in fertilising ability, may have made such tests less relevant to eventual pregnancy outcome.

Immunological investigations
In the infertile population as a whole, antisperm antibodies (ASAB) occurs in 5–10% of individuals (men more than women), but they are also present in about 2% of fertile men, most commonly IgG and IgA. IgM antibodies, because of their size, are rarely found in semen and if present may be associated with infection. Sperm bound IgA antibodies are associated with poor cervical mucous penetration, but this is not the case with sperm bound IgG antibodies. The presence of sperm antibody in the serum of either partner is probably associated with impaired infertility but the case has not been proved, so that routine testing for serum ASAB, although widely practised, is not recommended. Immunobead testing (IBT), however, against IgA and IgG in semen is recommended, although differences in analytical practice render comparisons of test results between centres unreliable. Assays that only identify serum ASAB may not be optimal because antibodies in the male genital tract may be of primary importance.

Screening for antibodies is performed on fresh samples and makes use of either the IBT method or the mixed antiglobulin reaction (MAR) test. The sample must contain at least 100 spermatozoa with progressive motility and the mucous, debris, and bacteria content must not be so high as to interfere with these tests.

The mixed antiglobulin reaction test
There is no gold standard for the diagnosis of immunological infertility but the MAR test is probably the first method of choice. This test identifies IgG on the spermatozoa. This is considered to be an adequate routine screening test because IgA antibodies almost never occur without IgG antibodies. Severely oligozoospermic and/or samples with greatly reduced motility are unsuitable for testing. The test is considered positive if 50% or more sperm have blood cells attached and weakly positive if 10–50% of the sperm have blood cells attached. In a negative test the sperm should swim freely between the aggregation of red cells. If the red cells do not aggregate together then the test is invalid and should be repeated. The test is considered of clinical relevance when > 50% agglutination is present.

The immunobead test
The IBT is one of the most widely used tests to detect ASAB, directly on sperm or indirectly in seminal plasma, cervical mucous, follicular fluid, and serum. The presence of IgG, IgA, and IgM antibodies on the sperm surface can be assessed simultaneously with this test. The test is considered to be positive when 20% or more of motile spermatozoa have immunobead binding, but only clinically relevant when 50% or more of the motile spermatozoa have antibody bound to them.

Other investigations
Karyotyping allows detection of problems such as Klinefelter’s syndrome (47, XXY), which accounts for many men presenting with non-obstructive azoospermia. Testing for cystic fibrosis carriers in both partners is now considered essential before couples are treated by ICSI if the man has congenital bilateral absence of the vas deferens. Reduced testosterone and raised LH concentrations are indicative of Leydig cell dysfunction. Additional investigations include a urine analysis, a urethral swab for chlamydia, and in some cases scrotal or transrectal ultrasound. Readers are referred to specialist texts for information on chromosomal investigations.

GOOD PRACTICE FRAMEWORK
Because reproductive potential is affected by age, pregnancy history, and medical, surgical, social, and environmental factors, laboratory investigations should take place within an appropriate clinically directed pathway. The general practitioner may play a central role in this pathway, with advice and referral to fertility specialists when indicated, because interpretation of the meaning of the various tests may sometimes be outside of his or her field of expertise.

APPENDIX 1 SUGGESTED PROTOCOL FOR ASSESSMENT OF SERUM PROGESTERONE
Measure serum progesterone seven days before expected period in all women. Interpret after next menstrual period known.

- if < 16 nmol/litre, repeat in another cycle. If consistently low refer to specialist.
- if > 16 nmol/litre but < 30 nmol/litre, repeat in another cycle. If the same or lower, may be indication for controlled ovarian stimulation so needs referral to specialist.
- if > 30 nmol/litre, consider as proof of adequate ovulation.
ECHO

Vδ2 cells depleted in both tuberculosis and HIV

A subset of circulating γδ T cell—Vδ—is depleted in both tuberculosis and HIV infections, irrespective of whether TB is active and whether the diseases are concurrent, Italian researchers have discovered.

Recent studies have suggested that γδ T lymphocytes have an important role in the immune response to Mycobacterium tuberculosis, but that the strength of the response varies according to the phase of infection and the immune status of the host.

CD4+, CD8+ and Vδ1 and Vδ2 T cell counts were analysed in the peripheral blood of 74 consecutive patients with TB, 20 of whom were co-infected with HIV. The results were compared with those from 39 blood donors and nine patients with symptomless HIV infection. The numbers of total lymphocytes and CD4+ cells were lower in the 54 TB patients not co-infected with HIV than in blood donors. But total γδ T cells and Vδ1 subsets were similar in both groups.

However, the percentage γδ T cells with the Vδ2 subset was significantly lower in TB patients than in either blood donors or patients with symptomless HIV infection. Responsiveness to the tuberculin skin test did not influence which γδ T cell subset predominated. The percentage of circulating Vδ2 cells was also lower in HIV positive patients, whether or not their TB was active, and comparable with levels in HIV negative patients.

The finding prompts the authors to ask whether the depletion of Vδ2 T cells might be explained by a pathological mechanism that is common to both infections.


References


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65 United Kingdom External Control Assessment Scheme. Sub-Fertility Laboratory, St Mary’s Hospital, Hathersage Road, Manchester, M13 OJH.


Optimal detection of Campylobacter spp in stools

In view of the importance of Campylobacter spp and related organisms in human disease, and the awareness of the under-reporting of these and related organisms in human disease, and in view of the importance of Campylobacter spp in stools, we read with interest the awareness of the under-reporting of these and related organisms in human disease, and...

Since 1977, the Red Cross Children’s Hospital in Cape Town, South Africa, has been isolating Campylobacter spp. In 1990, for cost containment reasons, the use of antibiotic containing selective media was discontinued, and the “Cape Town” protocol introduced. This protocol combines both membrane filtration on to antibiotic free blood agar plates and incubation in an H2 enriched microaerobic atmosphere (oxyd BR 38 (Oxoid, Basingstoke, UK) or BBL 70304 without catalyst (BBL, Kansas City, USA)). Although other workers have advocated filtration for isolation of Campylobacter, and related species from human stools using non-selective filtration, selective plating, and polymerase chain reaction (PCR) detection.

References
3. Le Roux E, Lastovica AJ. The Cape Town protocol was consistently superior for the isolation of campylobacteraceae. Differences in the prevalence of campylobacter may well exist between Cape Town and the UK, and the application of the Cape Town protocol in future UK studies, as has been suggested, should improve the campylobacter isolation rate and, hopefully, answer this question.

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CORRECTION


Dr C Williams’s address should have been Wrexham Maelor Hospital, Crewe Newydd Road, Wrexham, Clwyd LL13 7TD, UK.

UK NEQAS for Blood Coagulation Annual Scientific Meeting

21–25 June 2003, Sheffield Hallam University, Sheffield, UK
Further details: Timothy Al Woods, UK NEQAS for Blood Coagulation, Rutledge Mews, 3 Southbourne Road, Sheffield S10 2QN, UK. (Tel: +44 (0)114 267 3300; Fax: +44 (0)114 267 3309; Email: talwoods@coagqa.demon.co.uk)

Fourth International Symposium on Hormonal Carcinogenesis

21–25 June 2003, Palau de la Musica, Valencia, Spain
Further details: Tandria Price/Dr Jonathan J Li, Department of Pharmacology, Toxicology and Therapeutics, Mail Stop 1018, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160-7417, USA. (Tel: +1 913 588 4744; Fax: +1 913 588 4740; Email: tprice@kumc.edu; Website: http://www.kumc.edu/hormon cancers)

UK NEQAS for Leucocyte Immunophenotyping Annual Scientific Meeting

24–25 June 2003, Sheffield Hallam University, Sheffield, UK
Further details: June Pidd, UK NEQAS for Leucocyte Immunophenotyping, Rutledge Mews, 3 Southbourne Road, Sheffield S10 2QN, UK. (Tel: +44 (0)114 267 3600; Fax: +44 (0)114 267 3601; Email: ukneqas@btconnect.com)

ACP Management Course for Pathologists, 2003

10–12 September 2003, Hardwick Hall Hotel, Sedgfield, County Durham, UK
Further details: Ms Valerie Wood, ACP Central Office, 189 Dyke Road, Hove, East Sussex, BN3 1TL, UK. (Tel: +44 01273 777500; Fax: +44 01273 773103; Email: valerie@pathologists.org.uk)

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