

How the items making up any issue of *Bandolier* come together is a bit of a mystery. Increasingly it comes about that questions posed by readers are matched, in time, by evidence that emerges from systematic reviews or good quality trials. This issue seems more devoted to questions posed, but where the answers fail to arrive. Sometimes, though, the answers themselves pose problems.

Irritable bowel syndrome

IBS is common, difficult to diagnose, and with few effective remedies. Most people who have it don't even see a doctor, but it still costs the NHS about £50 million a year [1]. *Bandolier* is consistently asked for help, and consistently fails to find any good evidence.

We found one recent report providing foods for thought [2]. Twenty consecutive patients with persistent watery or loose stools 4-15 times a day for three months to 20 years (median one year) had only limited relief from previous conventional IBS therapies. Within three days of starting of starting treatment with histamine antagonist or proton pump inhibitor, the diarrhoea and urgency abated, with one to three formed stools a day and amelioration of symptoms. Five patients stopped treatment with prompt return of diarrhoea, again relieved by treatment.

Now as best *Bandolier* can judge there is no more evidence. Pharmaceutical companies making acid suppressants had not heard of this. That's it. There's no more. What do we do? At least acid suppressants are not grapefruit seed extract, and we know a lot about safety. But do we just wait for some trials?

References:

- 1 NE Wells, BA Hahn, PJ Whorwell. Clinical economics review. *Aliment Pharmacol Ther* 1997 11: 1019-1030.
- 2 B Dave, W Rubin. Inhibition of gastric secretion relieves diarrhea and postprandial urgency associated with irritable bowel syndrome or functional diarrhea. *Digestive Diseases and Sciences* 1999 44: 1893-1898.

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The views expressed in Bandolier are those of the authors, and are not necessarily those of the NHSE

TINNITUS AND MENIERE'S UPDATE

Bandolier is frequently asked about treatments for tinnitus and Meniere's disease, and occasionally trawls the literature to see if there is anything new. Depressingly there isn't. Three reviews published in recent years at least give an insight into the extent of research.

Randomised trials in tinnitus

One review [1] had a good search strategy using MEDLINE and found 69 randomised studies of drug and non drug treatments, 51 of which included a placebo arm. Positive studies were closely scrutinised for trial quality and validity. Common problems were inadequate controls, failure to measure the impact of tinnitus and treatment on patients, and small size. Positive studies were often small and their results were not always replicated by later, larger, studies.

There is no easy way of describing the results. Table 1 shows the treatments, the number of trials, and comments on the results. Those treatments demonstrating some benefit included alprazolam, tricyclics, and electrical stimulation over the mastoid. The caution is that we do not have solid evidence of effect, nor can we be sure of the size of the effect. But the rest we can probably dismiss.

Psychological treatments for tinnitus

It is always interesting to pick up two reviews which come to different conclusions. The first review [1] concluded that psychological interventions were ineffective. A review concentrating on psychological treatments [2] for tinnitus concluded that they were effective.

The difficulty is to know where the truth lies. The review of psychological interventions had a good search strategy, including specialist journals, and eventually used 18 for analysis, covering cognitive behavioural therapy, relaxation, hypnosis, biofeedback, educational sessions and problem solving. But it included non-randomised studies, and used effect size to describe the results, which makes it impossible to know what they were. *Bandolier* is suspicious.

The biggest problem is the size of the studies. Sixteen of 24 comparisons in the analysis were based on fewer than 30 patients. Three were based on more than 50 patients. This paper was full of statistics, and though there were some interesting comments on different outcomes, it is impossible to use the information other than a list of studies.

Evidence of efficacy from randomised trials for tinnitus

Treatment	Number of trials	Comments
Tocainide and related drugs	9	No evidence for any effect, and significant adverse effects
Lidocaine iontophoresis		No benefit
Carbamazepine	4	No benefit
Benzodiazepines	4	Alprazolam was effective in one trial said to be of good quality. Some benzodiazepines made tinnitus worse in some patients.
Tricyclics	4	Some evidence of minor benefit with nortriptyline and amitriptyline
Ginkgo	2	No benefit
Miscellaneous drugs	14	No evidence for any effect from a wide variety of other drugs
Psychotherapy	11	Mixed evidence of efficacy, with short-lived, small effects, probably clinically insignificant
Electrical/magnetic	6	Some evidence of electrical stimulation over the mastoid
Acupuncture	6	No benefit in any study
Masking	6	No evidence for any significant effect
Biofeedback	5	Mixed evidence of efficacy
Hypnosis	3	No evidence for any significant effect
Ultrasound	2	No evidence for any significant effect
Miscellaneous non drug	4	No evidence for any significant effect

Medical treatments of Meniere's disease

A review of MEDLINE between 1978 and 1995 was conducted to find papers relating to Meniere's disease [3]. Trials of all architecture were included and discussed, including animal experiments. The main clinical outcomes of treatments where the words double-blind are mentioned are shown in Table 2.

The only clear evidence is for betahistine, as reviewed in *Bandolier* 13. Our own searches found no new randomised trials in Meniere's disease since 1995.

Comment

Tinnitus is common, with between 1% and 2% having a tinnitus that plagues them all day and affects quality of life to

a severe degree. Aside from betahistine in Meniere's disease there seems little good evidence for effective treatments. Trials are often small, and with poor design, and there are many questions about appropriateness of outcomes. It is about time someone got this by the scruff of the neck, laid out appropriate conditions for valid trials, and found a medical research organisation to fund trials to give us some sensible evidence to be getting on with.

Reference:

- 1 RA Dobie. A review of randomized clinical trials in tinnitus. *Laryngoscope* 1999 109: 1202-1211.
- 2 G Andersson, L Lyttkens. A meta-analytic review of psychological treatments for tinnitus. *British Journal of Audiology* 1999 33: 201-210.
- 3 J Claes, PH van de Heyning. Medical treatment of Meniere's disease: a review of the literature. *Acta Otolaryngologica* 1997 Suppl 526:37-42.

Evidence of efficacy from double-blind trials for Meniere's disease

Treatment	Number of trials	Comments
Betahistine	5	Betahistine effective in controlling vertigo, dizziness or imbalance. Does not improve hearing levels
Diuretics	1	Effective in controlling vertigo, but no effect on hearing
Vaso-active drugs	1?	Less effective than betahistine
Aminoglycosides	0	
Salt restriction	0	
Steroids	0	
Other treatments	0	

INTERMITTENT CLAUDICATION TREATMENTS

Intermittent claudication is muscle pain on exercise relieved by rest. It is most often caused by atherosclerotic narrowing of the iliac and femoral arteries, often combined with lesions in distal arteries of the leg. It may affect as many as 5% of men over 50 years. For some the symptoms improve. For 10-20% they progress, and in perhaps one in 20 amputation is necessary because of a gangrenous limb.

Exercise therapy has been shown to be effective in increasing pain free walking time (*Bandolier* 52). Two new systematic reviews [1,2] examine additional aspects of medical management.

Search

Both reviews came from the same team in Padua and Amsterdam. Searching was English language medical literature using MEDLINE. One review [1] examined physical training, smoking cessation, pentoxifylline or nafronyl. The other [2] examined antithrombotic treatments.

Results

The results from both reviews are reviewed briefly.

Physical training [1]

There were seven randomised but open studies of physical training. The comparison was usually placebo tablets or usual activity, and training consisted of 30-60 minute training sessions several times a week for three to six months. Studies were small, the largest being about 40 patients.

Four studies (94 patients total) had information on pain free walking distance, which was increased by a mean of 139 metres (95% confidence interval 31 to 247 metres; Figure 1). The total walking distance was increased by 179 metres (60 to 298 metres).

Stopping smoking [1]

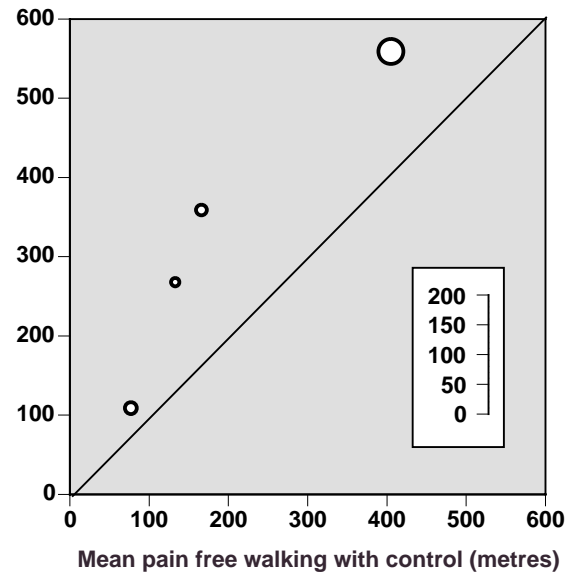
Only four non randomised studies on the effects of smoking cessation in 183 patients were found. Included patients were smokers on referral, or who had stopped smoking in the previous six months. There was no consistency in the results, which are probably uninterpretable.

Pentoxifylline [1]

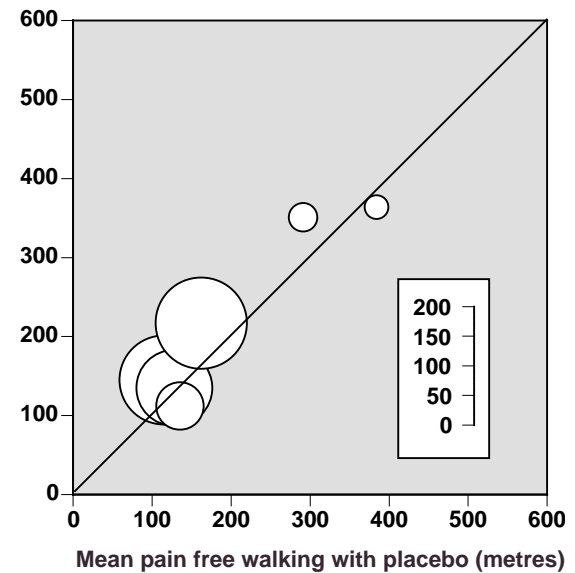
There were six randomised, double-blind studies (600 patients total) with information on pain free walking distance (Figure 2). The mean increase in pain free walking distance over two to six months on 400-1200 mg a day compared with placebo was 21 metres (1 to 41). The total walking distance was increased by 44 metres (14 to 74 metres) in seven studies.

Figures 1-3: Pain free walking distances with training, pentoxifylline and nafronyl

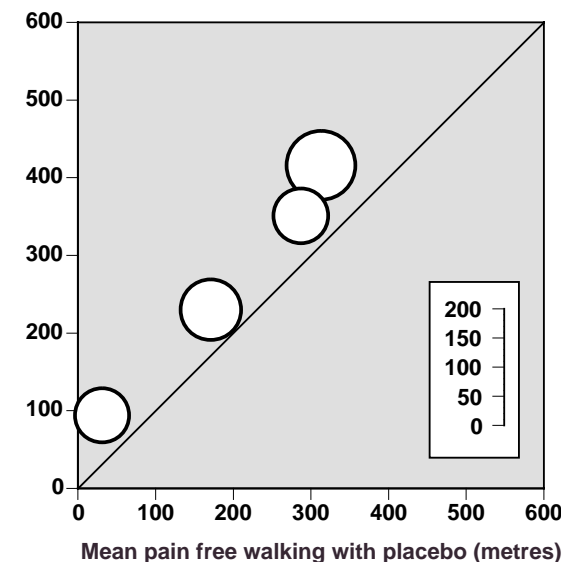
Mean pain free walking with training (metres)



Mean pain free walking with pentoxifylline (metres)



Mean pain free walking with nafronyl (metres)



Nafronyl [1]

Four randomised, double-blind studies (409 patients total) had information on pain free walking distance (Figure 3). The mean increase in pain free walking distance over three to six months on 400-800 mg a day compared with placebo was 59 metres (30 to 87). The total walking distance was increased by 71 metres (13 to 129 metres) in two studies.

Antithrombotics [2]

Studies of antithrombotics versus placebo or no treatment were generally small, and with few patients on any one treatment. Those with at least three studies and/or 200 patients in a comparison and which showed benefit included:

Indobufen: 400 mg a day over six to 12 months produced a mean increase in pain free walking distance of 451 metres and 74 metres in two trials with a total of 354 patients.

Low molecular weight heparin at 8,000 or 15,000 units a day for six months produced a mean increase in pain free walking distance of 53 metres (20 to 87 metres) in three trials with 135 patients.

Sulodexide at 600-1000 units a day for 70 days produced a mean increase in pain free walking distance of 113 metres (77 to 148 metres) in six trials with 209 patients.

Comment

Exercise training again appears to be a good buy for patients with intermittent claudication, as part of overall management. At least these reviews tell us what knowledge there is in some areas of treatment for this disorder. Gathering together the best available evidence at least tells us where we are, even if its not where we want to be.

Reference:

- 1 B Girolami et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl. Archives of Internal Medicine 1999 159: 337-345.
- 2 B Girolami et al. Antithrombotic drugs in the primary medical management of intermittent claudication: a meta-analysis. Thromb Haemost 1999 81: 715-722.

OXFORD MASTER'S PROGRAMME IN EVIDENCE-BASED HEALTH CARE

The Master's Programme has three part-time award bearing courses - a Post Graduate Certificate, a Postgraduate Diploma and an MSc. The aim of the Postgraduate Certificate Programme is to help health professionals by giving them the skills to find, appraise, and use evidence to make clinical and health management decisions. The programme is intended for professionals, clinicians, managers, planners, researchers and teachers. Students will:

- be graduates or will have successfully completed a professional training course have at least five years professional work experience in the health service

PRE-SCHOOL VISION SCREENING

Bandolier has been asked about the value of testing children for amblyopia, defined as a unilateral or, rarely, bilateral decrease of vision for which no obvious cause can be found on physical examination of the eye. The aim of pre-school vision testing in pre-school children is to detect a range of conditions, including amblyopia, refractive errors and non-cosmetic squints which cannot be detected without screening.

Screening issues

The basic principles of screening are that:

- ◆ The condition is common and disabling, the natural history is known and that there is a recognisable latent or pre-symptomatic phase.
- ◆ The screening test is reliable, valid and repeatable, is acceptable and easy to perform, is sensitive and specific and low cost.
- ◆ The treatment should be effective and available, and that there is an agreed policy on who to treat.

Are these conditions met for pre-school vision screening?

Systematic reviews

A systematic review with a heroic search strategy [1], say that they are not.

It found no studies that could document the natural history of squint, amblyopia or refractive errors in three to four year old children. What little information is available argues against the need to treat.

Another systematic review of vision screening tests for detection of amblyopia [2] looked for high quality studies meeting stringent criteria for evaluation of diagnostic tests. It found four studies, only one of which addressed traditional vision screening. In comparison with ophthalmologic examination the test had a sensitivity of about 12% and a specificity of 99% in a population with a prevalence of 6%.

- be able to bring to the proposed courses specific work-based health problems, about which they will be seeking evidence
- be able to combine intensive classroom learning with the application of the principles and practices of evidence-based health care within the workplace

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Randomised trials of treatment [2] were small in both number and size. None compared patching with no patching

Comment

It could hardly be claimed, even by the most enthusiastic supporter of pre-school vision testing, that there is any significant evidence that screening is effective. Clearly there are many more aspects than *Bandolier* has time for here, but again, the evidence in these other areas is slight.

Reference:

- 1 SK Snowden, SL Stewart-Brown. Preschool vision screening: results of a systematic review. CRD Report 9, NHS Centre for Reviews and Dissemination, April 1997.
 - 2 AR Kemper, PA Margolis, SM Downs, WC Bordley. A systematic review of vision screening tests for the detection of amblyopia. *Pediatrics* 1999 104: 1220-1222.
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LITHIUM AND HYPOTHYROIDISM

Bandolier is often asked about either the need for monitoring thyroid function in patients on lithium therapy, or how frequently it should be done, or both.

Systematic review

A review of the English language literature found on MEDLINE [1] reports the prevalence of overt hypothyroidism to be 8% to 15% in patients taking lithium, compared with about 1% in the general population. It suggests that baseline thyroid function should be assessed before starting lithium, with a symptom checklist at two-monthly intervals, and with laboratory tests three months after starting lithium treatment and thereafter every six to 12 months.

Age and sex

A survey of 209 patients with affective disorder from one catchment area [2] concluded that six female patients had thyrotoxicosis before starting treatment. Thereafter 20 patients developed hypothyroidism, 3% of men and 15% of women. No patient developed hypothyroidism within five years of starting treatment if lithium was started before the age of 50 years. There was a distinct trend for women patient over the age of 50 years to have increased risk of developing hypothyroidism.

The report suggests more frequent thyroid testing (every three months) for women aged over 45 or 50 years, with less frequent testing (every six or 12 months) for men and younger women.

Reference:

- 1 J Kleimer, L Altshuler, V Hendrick, JM Hershman. Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. *Journal of Clinical Psychiatry* 1999 60: 249-255.
 - 2 G Kirov. Thyroid disorders in lithium-treated patients. *Journal of Affective Disorders*. 1998 50: 33-40.
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DRE SCREENING FOR PROSTATE CANCER

Screening for prostate cancer is a topic that raises blood pressure more than the intellectual level of debate. Some people want it because of the old argument that finding and treating cancer early must be good. Others bring us back to earth by reminding us that the issues come down to many more men dying with prostate cancer than from prostate cancer. The issue is pussycats and tigers – tigers being the aggressive cancers that we do perhaps need to catch early. *Bandolier* has visited this before (issues 26, 39 and 43). But some newly published studies help clear the mind a bit.

If we are to screen, what population of men do we screen and what test do we use? A new meta-analysis [1] from Maastricht tells us how well digital rectal examination (DRE) does in unselected older men in primary care.

Search

MEDLINE and a specialist primary care database were searched electronically, and selected primary care journals hand searched without language restriction. Included studies had to compare DRE with biopsy or surgery as a reference diagnosis. Disease was usually excluded on the basis of a negative biopsy, and/or negative DRE combined with a negative PSA test or transrectal ultrasound. The study population had to be unselected with respect to prostate signs or symptoms.

Results

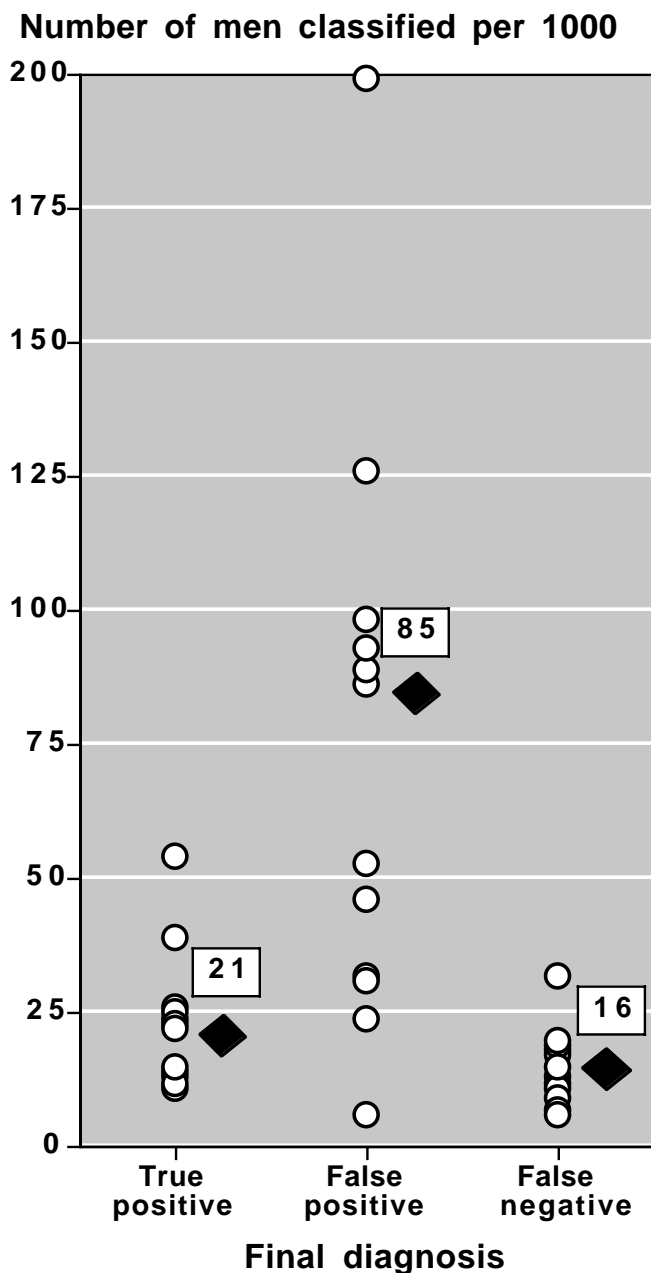
There were 14 studies with results on 21,821 men. The size of studies ranged between 315 and 6630 men. The lower age ranged between 45 and 60 years, and the upper age ranged between 70 and 90 years. The overall prevalence of biopsy or surgery confirmed prostate cancer was 3.7% (range 1.2% to 7.3%).

The paper provides information on a number of statistical outcomes. Thus in individual studies the likelihood ratio for a positive test ranged between 2.1 and 114. The negative predictive value was always above 95%.

Because *Bandolier* has problems with these statistical outcomes, the results of the studies are presented in a different way in the Figure. Studies were normalised to 1000 men, and the number calculated for:

- ◆ True positive: screened positive by DRE and with cancer shown by biopsy or surgery. In every 1000 men screened the average number screened positive and with cancer was 21 men (range 6 to 54).
 - ◆ False positive: screened positive by DRE and with no cancer shown by biopsy or surgery. In every 1000 men screened the average number with screened positive but without cancer was 85 men (range 6 to 301).
-

Figure: Results of individual trials and weighted average (diamond) for DRE positive with cancer (True positive), DRE positive without cancer (False positive) and DRE negative with cancer (False negative)



◆ False negative: screened negative by DRE and with cancer shown by biopsy or surgery. In every 1000 men screened the average number with who screened negative but who actually had cancer was 16 men (range 4 to 32).

So for every man detected by DRE and biopsy as truly having prostate cancer, four would be screened positive without actually having cancer, and one man with cancer would be missed.

Primary care group

These numbers can be applied to an average primary care group of 100,000 people. If screening with DRE were applied to all men over 45 years (about 17,000 of them), that would mean 359 cancers detected, 274 cancers missed, and 1454 men with positive DRE who would have to be biopsied to exclude them actually having cancer.

Moreover

Actually, it could be worse than this. Firstly we know that the usual sextant biopsy probably used in most of these studies has been shown itself to miss 35% of prostate cancers (*Bandolier* 43). We also know that the PSA test, used to exclude cancer in a number of the studies, is normal in about 40% of men with cancer (*Bandolier* 26). It is likely that the number of missed cancers is therefore higher than that suggested by the paper, perhaps missing as many cancers again.

If that were the case, screening for prostate cancer with DRE in primary care would mean that for every case of cancer found, two would be missed and four men unnecessarily sent for further investigation.

Cost

The implication of screening for prostate cancer on health service budgets is huge. An exercise to establish the actual and projected costs of screening with PSA in Canada [2], suggested that screening cost about £50 per man screened when the costs of treatment and the harms of treatment were added in.

Comment

Few of the studies discussed the method of digital rectal examination used or the sort of result from the digital rectal examination that constituted a positive test. The review considered a non-enlarged, smooth, symmetrical prostate with normal consistency to be normal, and test results were recalculated using this criterion where it was possible to do so. The review, concentrating on men without prostate problems, cannot speak about the usefulness of DRE for diagnosing prostate cancer in men with prostate symptoms.

Bandolier found the statistical outcomes unhelpful, which is why we calculated the results on the basis of actual numbers of men classified correctly or incorrectly, on the basis of 1000 men and a primary care group. This seems to be much easier to understand than sensitivity and specificity, or other ways of expressing results of diagnostic tests. As shown in *Bandolier* 61, most doctors seem to agree with us that we need new ways of expressing and using test results.

The arguments for screening for prostate cancer are moot, and digital rectal examination alone would be unlikely to be used. When more sophisticated methods are evaluated, like PSA or newer laboratory tests, it will be interesting to see how many men are correctly and incorrectly diagnosed.

Reference:

- 1 A Hoogendam, F Buntinx, HCW de Vet. The diagnostic value of digital rectal examination in primary care screening for prostate cancer: a meta-analysis. *Family Practice* 1999 16: 621-626.
- 2 MD Krahn, A Coombs, IG Levy. Current and projected annual direct costs of screening asymptomatic men for prostate cancer using prostate-specific antigen. *Canadian Medical Association Journal* 1999 160: 49-57.

INTRACRANIAL ANEURYSMS

There is an irregular verb *Bandolier* uses in its office. It's declension is: "I despair, you can't understand it either, he has another paper on his CV so why worry!" Almost every paper to which this verb applies gets filed in the round receptacle in the corner.

Perhaps that is unfair. A systematic review of critical appraisal skills training [1] provides some evidence that critical appraisal is of benefit. Though it does not have much to work with, knowledge, and attitudes to the medical literature benefit from training. So while *Bandolier* likes to concentrate on the good, rather than the bad or just plain ugly, occasionally a paper begs to be held up as one to be used for critical appraisal training.

Search

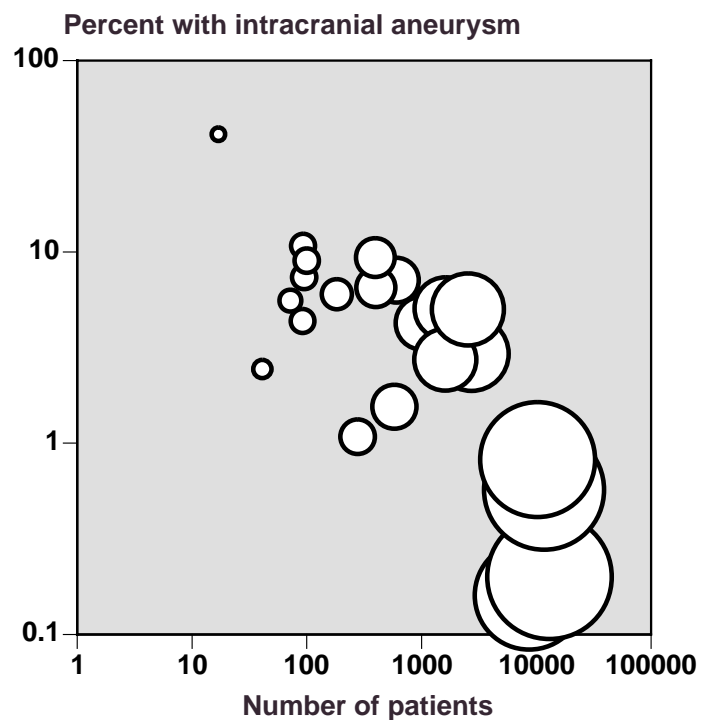
This one [2] used MEDLINE to find papers on prevalence and natural history of intracranial aneurysms, plus reference lists.

Eligible studies had to give numbers of patients studied and the number with aneurysms, and it had additional, apparently reasonable, conditions for autopsy and angiography studies. Indications for angiography were family history of subarachnoid haemorrhage, autosomal dominant polycystic kidney disease, atherosclerosis, suspected pituitary tumour, brain tumour, or other.

Results

The frequency of incidental aneurysms varied considerable between different types of study (Table 1). The reasons are not given. While there was an inverse relationship between

Figure: Percent of patients with intracranial aneurysms in each study plotted against the total number of patients included



size and incidence (Figure), this was an artefact. The main reasons lay in the method for estimating the aneurysm, or the population, or both. For instance, one of the large retrospective autopsy studies examined aneurysms in an autopsy file of a hospital between the years 1914 and 1956. The prospective angiography studies examined small populations with particular disorders, like a family with a history of subarachnoid haemorrhage. What is frustrating is that the only source of information on the populations studied is the titles in the references.

Table 1: Intracranial aneurysm by type of study

Type of study	Number of studies	Number of patients	Percent with aneurysm
Restrospective autopsy	4	43676	0.4
Prospective autopsy	4	5943	3.6
Restrospective angiography	6	2934	3.7
Prospective angiography	9	3751	6.0

Table 2: Intracranial aneurysm by indication for angiography

Indication	Number of studies	Number of patients	Percent with aneurysm
Family history	3	476	9.5
Autosomal dominany polycystic kidney disease	3	202	10.0
Atherosclerosis	5	3676	5.3
Pituitary tumour	2	183	6.0
Brain tumour and other	5	2052	2.3

But useful information is there. For instance, 93% of the aneurysms were 10 mm or less. High rates were found with some conditions and not others (Table 2). Risk of rupture was higher with large aneurysms, in women, people over 60 years, with symptoms, and in the posterior circulation.

Comment

Perhaps *Bandolier* is a bit harsh, but we've read this paper many times before understanding it. Like all systematic reviews, at least it provides a start if you think you can do better.

Reference:

- 1 R Taylor et al. A systematic review of the effectiveness of critical appraisal skills training for clinicians. *Medical Education* 2000 34: 120-125.
- 2 GJ Rinkel, M Djibuti, A Algra, J van Gijn. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke* 1998 29: 251-256.

ARE BREAST IMPLANTS SAFE?

About 80% of silicone breast implants are for cosmetic purposes, and 20% for breast reconstruction after surgery, mainly for cancer. A review of their safety [1] does not include details of any formal searching. Women who have breast implants, perhaps reflecting the fact that they are predominantly for cosmetic purposes, are different from their sisters who do not have implants. They are much less likely to be obese, drink more, be younger at first pregnancy and first birth, have a history of terminated pregnancies, to have used oral contraceptives, have more sexual partners and use hair dyes.

The finding of high levels of silicone in women with implants does not substantiate a causal relationship between silicone and reported disease. Silicone is a common mineral, and is used in food, beverage and cosmetic industries. It is used in medicine, and over a lifetime an insulin-requiring diabetic may inject up to 50 grams of silicone, and have substantial bodily exposure to silicone. Some of the suspected problems with silicone breast implants have been looked at in detail:

Capsular contraction

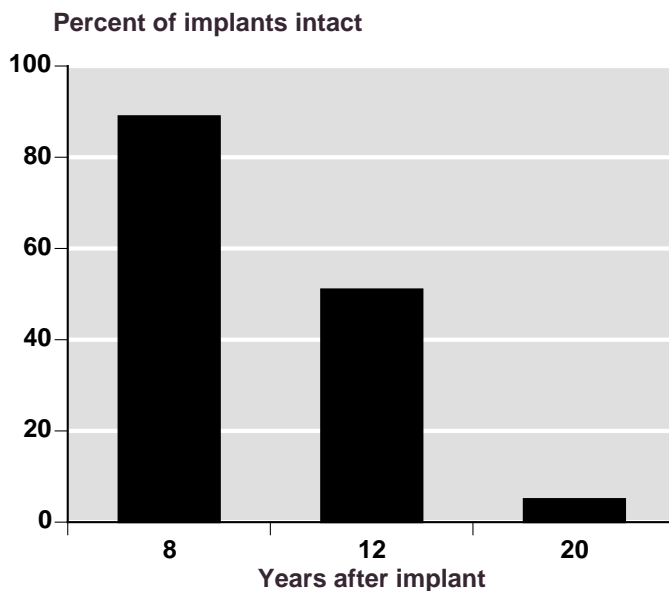
Formation of a capsule around an implant is part of the inflammatory response to a foreign body. Contracture of the capsule results in moderate to extreme hardening of the breast, tightness, pain or deformity. The overall incidence was 17% in 1454 breasts in 749 women, with five-year rates of 12%, 34% and 30% for cosmetic, cancer or cancer prophylactic surgery. It also occurs with saline implants.

Implant rupture

The proportion of implants expected to be intact is 89% after eight years, falling to 5% after 20 years (Figure).

Cancer

No epidemiological study has found an increased risk of



breast cancer in women with breast implants compared to those without.

Interference with breast cancer detection

Current advice from the American College of Radiology says that adequate breast examinations can be achieved with currently available mammographic techniques.

Autoimmune disease

The paper examines the association of silicone with immunological reactions and links with connective tissue disorders. The epidemiological information was almost universally negative. One, large, study of health professionals found a very small, statistically significant increased risk of connective tissue diseases in women with breast implants. The weight of evidence was against the implants causing any generalised disease.

Comment

This paper is let down because it does not have a search strategy, although there are 77 references. For anyone wanting to find the best information for themselves or patients on risks associated with breast implants, this would be a good place to start.

Reference:

- 1 PC Gerszten. A formal risk assessment of silicone breast implants. *Biomaterials* 1999 20: 1063-1069.

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