Clinical review

New approaches to preventing restenosis

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For over a quarter of a century percutaneous coronary interventions have been used to treat patients with coronary artery disease, yet restenosis continues to be a problem. This review discusses the advances being made to overcome restenosis, particularly the development of drug eluting stents

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Andreas Gruntzig pioneered percutaneous transluminal coronary angioplasty in 1977.¹ Since then, percutaneous coronary interventions have revolutionised the treatment of patients with symptoms of coronary artery disease, sparing them the need for surgical revascularisation. In the United States, the number of percutaneous interventions performed each year is nearly double that of coronary artery bypass surgery.^{w1} There have been three phases in the evolution of percutaneous interventions (see box 1), but in each restenosis has been a problem. It seems the next (and optimistically the final) phase is the development of drug eluting stents—that is, stents used for the local delivery of drugs (table).

Sources and selection criteria

The information in this review is based on the results of a Medline search using the key words coronary angioplasty, restenosis, instent restenosis, drug eluting stents, and intracoronary brachytherapy, and articles from the authors' personal collection. Cross references and related articles were accessed when necessary.

Restenosis

Restenosis is the maladaptive response of the coronary artery to injury. The simplest and most widely used definition of restenosis is a diameter stenosis of 50% at follow up. Restenosis occurs in 20-50% of patients after balloon angioplasty and in 10-30% of patients receiving a stent. Three distinct processes are involved—recoil of the vessel, neointimal proliferation, and early thrombus formation. The relative contribution of each of these depends on the type of injury. About three quarters of the lumen loss after balloon angioplasty is due to vessel recoil and the rest to neointimal proliferation,² whereas coronary stenting virtually eliminates vessel recoil, and restenosis is largely due to neointimal proliferation. Growth factors and cytokines are the major stimuli for proliferation of smooth muscle cells after an artery is injured, when deposition of platelets, leucocyte infiltration, expansion of smooth muscle cells, deposition of extracellular matrix, and re-endothelialisation occur. The platelets release platelet derived growth factor, transforming growth factor, epidermal growth factor, and thrombin,

Summary points

Restenosis is a common problem after percutaneous coronary interventions, depending on patient characteristics, lesion morphology, and the type of intervention

Coronary stenting is the only intervention that has reliably and consistently reduced restenosis in coronary lesions

Near zero per cent restenosis rates have recently been achieved with antiproliferative drug eluting coronary stents

Recurrent stenosis after treatment of instent restenosis is common

Adjuvant treatment with intracoronary γ and β radiation is the most effective currently available means to prevent recurrent stenosis after the treatment of instent restenosis

Modifying gene expression using antisense therapies or gene transfer will play an important part in the prevention of restenosis

which stimulate the migration, growth, and division of smooth muscle cells.^{w2 w3} Within the smooth muscle cell, cyclin dependent kinase and cyclins (regulators) drive the cell from one phase to another: G0, resting phase; G1, growth phase; S, replication of DNA; G2, preparation for division; and M, cell division. Cyclin dependent kinase has been described as the engine and the cyclins as the gearbox, determining whether the engine will run in the steady state or drive the cell forward in the cell cycle. Together they regulate cell

Box 1: Evolution of percutaneous interventions

- Phase 1 (1977-87): simple balloon angioplasty
- Phase 2 (1988-92): new device angioplasty
- Phase 3 (1993-2002): stent revolution

Additional web
references
(w1-w53) and
tables appear on
bmj.com

Restenosis and in-stent restenosis, 1977-2002

Year and procedure	Indications	Restenosis rate (%)	New problem	Solution
1977-87: percutaneous transluminal coronary angioplasty	Simple lesions, chronic syndromes	30-50	Restenosis, subacute closure	Stent
1988-92: Newer devices—Rotablator, excimer laser coronary angioplasty, directional coronary atherectomy	Complex, calcific, tortuous, bifurcations, left main, multiple lesions	50	Restenosis; restenosis 50-70%	Intravascular ultrasound guided use
Stents	Acute coronary syndromes	20-30	Restenosis, subacute thrombosis, in-stent restenosis	High pressure, anticoagulation
1993-2002: newer stents (biodegradable, covered, radioactive, intravascular ultrasonography)	Carotids, iliacs, renals, saphenous vein grafts, abdominal aortic aneurysms direct, rupture	10-20	In-stent restenosis, re-restenosis 50-70%	Improved designs and material, radiation
1995-2002: brachytherapy—photodynamic therapy, ultrasonography, cryotherapy, cutting balloon	In-stent restenosis	<10	Restenosis, re-restenosis 10% late thrombosis, edge failure, geographical miss	Prolonged antiplatelets
2002: eluting stents—drugs, gene	Simple lesions, chronic syndromes, some complex lesions	0-5	?Delayed restenosis	?Ultimate angioplasty

cycle progression and migration of smooth muscle cells (figure).

Clinically significant restenosis generally occurs between one and three months after balloon angioplasty. Most patients present with typical angina, usually within four months of the procedure—restenosis is much less likely to be the cause of symptoms after six months. With coronary stenting the presentation is delayed further by about one to three months.^{3 w4}

Prediction of restenosis

Restenosis depends on several factors (box 2). The risk of restenosis is increased in patients with diabetes mellitus, acute coronary syndromes, and, importantly, an inherent predisposition to restenosis.^{4 w5 w6} The increased restenosis rate among patients with diabetes is attributed to endothelial dysfunction, dysregulation of growth factor production, and increased platelet aggregability and thrombogenicity.^{w7} In acute coronary syndromes, vascular injury worsens the existing thrombogenic milieu and promotes cellular proliferation. Evidence of a predilection to restenosis comes from observations of a bimodal pattern of distribution of stenosis after angioplasty and the presence of restenosis at another treated site.^{5 w8} This predisposition might be mediated by genetic factors. Putative abnormalities are deletion polymorphisms of the gene encoding angiotensin converting enzyme, abnormalities in the expression of genes encoding the platelet Gp IIb-IIIa receptors, and some specific apolipoprotein E genotypes.^{w9 w10 w11} The most important lesion characteristics predicting restenosis are a small vessel diameter and a long lesion length.^{6 7 w12 w13} A large minimum lumen diameter after stenting reduces the rate of restenosis—that is, “bigger is better.”^{w13}

Prevention of restenosis

Drugs

Several drugs, including those with antiplatelet, anti-thrombotic, antiproliferative, and anti-inflammatory properties, have been used to prevent restenosis, but except for probucol and prednisolone their contribution has been largely disappointing.^{w14 w15} The role of

drugs in preventing restenosis is likely to be small because the principal mechanism of restenosis after balloon angioplasty concerns remodelling of the artery. These drugs might have a role in preventing neointimal proliferation after stenting.

Coronary stents

Stents produce the largest net gain in lumen diameter because they achieve an immediate large gain with modest later loss of diameter. The Belgian Netherlands stent study (BENESTENT) and the stent restenosis study (STRESS) showed that stents reduce restenosis rates after balloon angioplasty.^{8 9} These studies were conducted on “ideal” lesions, however, and higher restenosis rates have occurred with more complex lesions. Several materials, coatings, and designs have been developed in the quest for the ideal stent (see table A on bmj.com). Most have shown little success, except for drug eluting stents.

Drug eluting coronary stents

Using a coronary stent for local delivery of drugs combines scaffolding with targeted drug action. Although initial research and clinical trials concentrated on sirolimus and paclitaxel, numerous agents with antiproliferative properties are currently under investigation (see table B on bmj.com).

Inhibition of neointimal formation by sirolimus impregnated stent

Box 2: Predictors of restenosis**Patient factors**

- Restenosis at another treated site
- Diabetes mellitus
- Intervention in acute coronary syndromes

Lesion characteristics and procedural variables

- Diameter of vessel
- Length of lesion or stent
- Minimum lumen diameter before stenting
- Minimum lumen diameter after stenting ("bigger is better")
- Ostial lesions
- Saphenous venous grafts
- Total occlusions

Sirolimus

Sirolimus (Rapamycin; Wyeth-Ayerst, PA, USA), a macrolide antibiotic with potent antifungal, immunosuppressive, and antimitotic properties, is produced by *Streptomyces hygroscopicus*, an actinomycete found in soil. It is used to prevent the rejection of renal transplants, but its systemic use is limited by the side effects of hyperlipidaemia and thrombocytopenia.^{w16} Stents are coated with a polymer containing low dose sirolimus then a layer of drug-free polymer, which serves as a barrier to diffusion. The polymer acts as a reservoir for sirolimus, allowing gradual elution of the drug (see figure). Sirolimus downregulates cytokine dependent kinase mTOR (mammalian target of rapamycin), thus preventing progression from the G1 phase (cell growth) to the S phase (DNA replication).^{10 11 w17} Sirolimus is only effective when bound to sirolimus binding protein (FKBP), present only on smooth muscle cells and lymphocytes, thereby providing important targeting.

In the initial pilot study of sirolimus (30 patients), the stent virtually eliminated angiographic and ultrasonic evidence of neointimal proliferation.^{12 w18} No in-stent or edge restenosis (restenosis within the stent or within 5 mm proximal and distal to the stent edges) was noted, and no major complications occurred. In the randomised study with the sirolimus eluting Bx velocity balloon expandable stent in the treatment of patients with de novo native coronary artery lesions (RAVEL) study (238 patients), no restenosis was observed in the sirolimus stent group compared with 27% of patients in the uncoated stent group.¹³ In the US arm of the SIRIUS study, 9% of patients in the sirolimus stent group showed angiographic evidence of restenosis at nine months compared with 37% in the uncoated stent group.^{w19} Revascularisation of the target lesion was reduced from 17% to 4%. There was no increase in subacute or late thrombosis. These results were all the more significant because many patients in this study were at a high risk of restenosis (patients with diabetes, those who had multivessel angioplasty, and those with overlapping stents). The Food and Drug Administration has recently approved the clinical use of sirolimus eluting stents in the United States.

Paclitaxel

Paclitaxel was originally isolated from the bark of the Pacific yew. It is an antineoplastic agent, currently used to treat ovarian cancer. Paclitaxel enhances the assembly of microtubules that interrupt proliferation, migration, and signal transduction. It is incorporated into a fast release carrier system on the stent. Trials of paclitaxel coated stents have shown significant reductions in restenosis. The pacliTAXel-eluting Stent (TAXUS I) trial showed no restenosis in the paclitaxel stent group at 12 months compared with 10% for the standard stent group.¹⁴ This difference was reflected in the revascularisation of the target lesion in both groups (0% v 10%). The major adverse cardiac event rate at one year was also considerably reduced (3% v 10%). Results were maintained at 24 months. The TAXUS II trial confirmed the reduction in restenosis.^{w20} Similar results were observed in the European evaluation of paclitaxel eluting stent trial (ELUTES).^{w21} In the recently published Asian paclitaxel eluting stent clinical trial (ASPECT), angiographic restenosis decreased from 27% in the uncoated stent group to 4% in the paclitaxel stent group, due to a dose dependent decrease in neointimal proliferation.^{w22} No increase in subacute stent thrombosis (thrombosis occurring between 48 hours and two weeks after stenting) or restenosis at the edges of the stent has been reported in published randomised trials. However, late thrombosis has been reported after stopping antiplatelet therapy.^{w23} Some concern has been expressed that inflammation of the intima might occur at higher doses. Nevertheless, it is clear that drug eluting stents will be increasingly used for the prevention of restenosis because they nearly eliminate neointimal proliferation with little untoward effect and without the need for special expertise or instrumentation.

Biodegradable stents

The Japanese Igaki-Tamai stent is made of poly-L-lactic acid and takes 18-24 months to biodegrade. The scaffolding prevents abrupt vessel closure in the acute phase and vessel recoil within six months. Clinical results are available for 15 patients, showing no major complications and a restenosis rate of about 10%.^{w24} The stent is being evaluated further.

Debulking devices

The occurrence of restenosis is reduced when larger minimum lumen diameters are achieved after stenting. This makes a case for the use of debulking devices to mechanically reduce plaque volume. Early trials comparing directional coronary atherectomy with balloon angioplasty showed an increased mortality and Q wave infarction with atherectomy.^{15 w25} Subsequently, strategies to optimally debulk combined with adjunctive balloon angioplasty to achieve the largest possible lumen diameters were tested against conventional balloon angioplasty.^{16w26} Less restenosis was shown with directional coronary atherectomy compared with plain balloon angioplasty, but there was no difference in revascularisation of the target vessel at one year. Further, this benefit came at the cost of a higher incidence of increases in periprocedural myocardial enzymes. This failure to show consistent benefit from debulking has been attributed to the late loss in lumen diameter being proportional to the acute gain after the

procedure (device “taxing”). A synergistic approach using directional coronary atherectomy and coronary stenting might have a role in reducing restenosis rates in complex lesions.^{w27 w28}

Gene therapy

Vascular gene therapy can potentially control cellular growth related restenosis by modifying gene expression. Antisense oligonucleotides can be used to block gene expression by binding segments of specific mRNA with complementary DNA sequences. In a porcine model of restenosis, intramural delivery of specific antisense oligonucleotides completely eliminated c-myc expression and dramatically reduced neointimal proliferation.^{w29} An alternative approach is by transfer of genes, which have beneficial antiproliferative effects (for example, genes for endothelial nitric oxide synthase (eNOS) and vascular endothelial growth factor). Gene transfer has mostly been achieved using adenoviruses as vectors, although plasmid DNA and retroviruses have also been used. Animal studies with gene transfer have shown marked inhibition of neointimal proliferation; phase I studies in humans are under way.^{w30}

Intracoronary radiation

The role of intracoronary radiation in preventing restenosis in de novo lesions is not entirely clear. Although one study showed a dose dependent decrease in the rate of restenosis after angioplasty, data from two studies in the United States were not favourable.^{17 w31 w32}

Instant restenosis

Instant restenosis is due largely to neointimal proliferation. A classification for instant restenosis has been developed, depending on the degree and distribution of the hyperplastic neointima.¹⁸ Broadly, instant restenosis can be focal or diffuse. Therapeutic success is dictated by the volume and extent of the neointima. Focal lesions respond much better than diffuse ones.

Balloon angioplasty

In contrast to the atherosclerotic plaque in de novo lesions, the hyperplastic neointima is relatively less compressible, and therefore the emphasis has been on debulking rather than on plaque compression to prevent recurrent stenosis. Nevertheless, balloon angioplasty has been used extensively. The occurrence of restenosis in this setting largely depends on whether the restenosis is focal or diffuse. The recurrent restenosis rate with diffuse lesions has been shown to be twice that of focal lesions (63% *v* 31%, respectively).^{w33} However, the recent angioplasty versus rotational atherectomy for treatment of diffuse instant restenosis trial (ARTIST) suggests that even for diffuse lesions balloon angioplasty is better than rotational atherectomy.¹⁹ Plain balloon angioplasty is also likely to be successful in patients with restenosis due to poorly apposed stent struts, where luminal gain depends more on additional stent expansion than tissue compression.^{w34} A meta-analysis concluded that balloon angioplasty should be the procedure of choice when a good immediate outcome can be expected, because the nine month major adverse cardiac event rate is virtually identical

with all forms of treatment.^{w35} Additional stenting within the region of instant restenosis (“stent sandwich”) improves immediate angiographic outcomes, but long term results are poor.^{w36 w37}

Cutting balloon angioplasty

Cutting balloon angioplasty utilises a standard balloon catheter with three or four microblades (depth 0.18 mm, thickness 0.70–0.76 mm). The blades, attached longitudinally and folded within the balloon, are exposed on inflation and cut the neointimal tissue, facilitating plaque compression. They also help to anchor the balloon to the neointima (standard balloons tend to slip proximally or distally during inflation). Cutting balloon angioplasty for instant restenosis is associated with lower rates of revascularisation of target lesions and restenosis.^{w38–w40} At many centres, cutting balloon angioplasty combined with intracoronary radiation is the treatment of choice for instant restenosis.

Debulking devices

Rotational atherectomy

Rotational atherectomy utilises a high speed (150 000–200 000 rpm) diamond tipped drill, which effectively removes hyperplastic neointima and results in a larger minimum lumen diameter compared with balloon angioplasty. The promising early results (20% restenosis) of the randomised trial of percutaneous transluminal coronary angioplasty versus rotablator for diffuse instant restenosis (ROSTER) could not be reproduced in the angioplasty versus rotational atherectomy for treatment of diffuse instant restenosis trial (ARTIST), which showed a worse outcome for rotablation.^{19 w41} One possible reason for this discrepancy is that the low pressure used for inflation of the balloon after rotablation led to little increase in the stent diameter. Presumably high pressure inflation would resolve this.

Directional coronary atherectomy

Directional coronary atherectomy effectively removes neointima, with about a third of patients requiring revascularisation of target lesions at 10 months.^{w42} However one meta-analysis showed that at nine months the major adverse cardiac event rates with directional coronary atherectomy did not differ significantly from other procedures.^{w35} Further, activation of the cutter through stent struts may disrupt stent integrity or create sharp edges that puncture balloons.

Intracoronary radiation (brachytherapy)

A more recent approach to instant restenosis is intracoronary radiation or brachytherapy, on the grounds that it may control the excessive proliferative response and limit neointima formation, analogous to low doses of ionising radiation to treat benign proliferative disorders such as keloids, heterotopic bone formation, and pterygia.^{w43} Different isotopes on various platforms have been used to develop practical systems for endovascular brachytherapy. The platforms are catheter based systems such as line source wires, radioactive beads (delivered hydraulically), and balloons filled with radioactive gas or liquid, or stents incorporating γ (low energy, high penetration) or β (high energy, low penetration) emitters.

The first intracoronary brachytherapy procedure in humans was performed in Caracas, Venezuela in 1994.^{w44} Endovascular brachytherapy has since been tested in over 5000 patients, leading to approval by the Food and Drug Administration for the treatment of in-stent restenosis with both β and γ radiation.^{w45}

Of the trials for the treatment of coronary in-stent restenosis by brachytherapy (see table C on bmj.com), the important ones are catheter based radiotherapy to inhibit restenosis after coronary stenting (SCRIPPS I), intracoronary gamma radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis (WRIST), and localised intracoronary gamma radiation therapy to inhibit the recurrence of restenosis after stenting (GAMMA I).^{20 21 w46} Initiated at the Scripps Clinic in March 1995, SCRIPPS I tested the efficacy of iridium-192 (γ source) in 55 patients with restenosis. At follow up, the patients who received radiation had better mean minimum lumen diameters, less late loss of lumen, and lower restenosis rates. The WRIST trial randomised 100 patients with in-stent restenosis and 30 patients with in-stent restenosis in saphenous vein grafts to ¹⁹²Ir or placebo. Restenosis was significantly reduced, particularly in patients with diabetes and those with vein grafts. Similarly, in the GAMMA I study on 252 patients, the primary end point—death, myocardial infarction, and the need for repeat revascularisation of the target lesion during nine months of follow up—occurred in 53 patients assigned to placebo (44%) and 37 patients assigned to ¹⁹²Ir (28%). Similar results have been observed with β radiation in the proliferation reduction with vascular energy trial (PREVENT) and in-stent hyperplasia inhibition with beta in-stent trial (INHIBIT).^{22 w47}

Two important complications related to brachytherapy are edge restenosis (“candy wrapper” effect) and the risk of late thrombosis. Edge restenosis was first noted with radioactive stents and is possibly the result of radiation dose “fall-off” at the edges of the stent combined with vessel wall injury from inflation of the balloon outside the stent margins. Edge restenosis may be prevented by avoiding the “geographic miss,”—that is, a portion of the vessel that has undergone injury during the procedure, but has not received the intended dose of radiation. The likelihood of geographic miss can be decreased by radioactive coverage of an adequate length of the vessel.^{w48 w49}

Delayed (after one month) thrombosis may occur in up to 9% of patients receiving additional stents at the time of radiation.²³ Therefore, such repeat stenting (stent sandwich) is discouraged. Further, a long course (more than six months) of antiplatelet therapy is recommended for all patients undergoing brachytherapy. Such treatment has reduced the risk of late thrombosis to that of the control population.^{w50}

Drug eluting coronary stents

Preliminary data on a paclitaxel coated stent has shown a high major adverse cardiac event rate, which was largely due to the need for repeat revascularisation of the target lesion.^{w51} The potential for improved results with drug eluting stents in the treatment of in-stent restenosis is being explored.

Additional educational resources

Reviews

O'Neill WW, Leon MB. Drug-eluting stents: costs versus clinical benefit. *Circulation* 2003;107:3008-11.
Lemos PA, Serruys PW, Sousa JE. Drug-eluting stents: cost versus clinical benefit. *Circulation* 2003;107:3003-7.
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Website

tctmd (www.tctmd.com)—an industry supported website, providing useful information on topics in interventional cardiology.

Information for patients

Cypher, sirolimus eluting coronary stent (www.cypherusa.com/patient)—Patient section of Cordis Corporation's sirolimus eluting stent website. Provides useful general information about restenosis and drug eluting stents.

The future

Drug eluting coronary stents will be increasingly used in clinical practice despite their high initial cost (about three times that of a bare metal stent) because the cost is likely to be compensated for by the reduced need for repeat revascularisation. The costs of stents should go down as more manufacturers enter the market, especially from Asia. It is anticipated that under 5% of patients who undergo multivessel angioplasty will need repeat revascularisation compared with the current 14-16%. This is expected to at least equal, if not better, the outcome with coronary artery bypass surgery for patients with multivessel disease, even in those with diabetes. This will be tested in the arterial revascularisation therapies (ARTS II) study.²⁴ Intracoronary brachytherapy will remain the best treatment for diffuse or refractory in-stent restenosis^{w52} until drug eluting stents are proved useful for this indication or until an efficient and reliable antiproliferative genetic therapy becomes available.

Contributors: All authors were involved in the preparation of the manuscript and in the revision process. BB will act as guarantor.

Funding: None declared.

Competing interests: None declared.

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(Accepted 3 July 2003)

Shy and retiring

Talk to any colleagues in the medical profession of a certain age, and, sooner or later, the conversation will turn to retirement. Everyone has looked up the pension tables thoughtfully sent out by the NHS to clinicians who reach the half century mark, and we each privately estimate when the fallout from stress, political interference, arguments with the chief executive, lack of parking space, etc, will outweigh the financial pressures of school and university fees, mortgage repayments, expensive habits, etc, and take action accordingly.

"Ah, retirement," we all say to ourselves, with a vision of the Nirvana that is to come. Well, I crossed over a few months ago—all carefully planned and with no sudden rush to the finishing line:

"How is retirement?" my colleagues ask when I see them on forays back into hospital to deal with the letters that still keep coming in.

"It's ... um, well, er. I don't know really."

"Don't know?" they echo. What can I mean? Has the break in routine made me go soft in the head?

I try to dig myself out of this hole: "It's just, actually I still seem to be so busy."

"Of course you're busy," they reply tartly. "Everyone says they are busy when they retire."

Yes, I know, but my busy things still seem to be the sort that I don't particularly want to do. When you retire you spend lots of time doing nice things, don't you? I am still doing the tricky bits—all the things I used to be able to get out of or put off because I was working full time. In any case, it takes time to feel retired: that little mental command nodule that we all have to push us through the days doesn't switch off easily, and if you still feel that somehow you ought to be working, it is almost as bad as the real thing.

Then there is the next question that always follows: "What are you going to do with yourself now you're retired?"

A reasonable question, and, of course, most of us have some plans or at least a "wish list," but it is all rather vague at first so this answer, too, is unsatisfactory. "Well, I will travel a bit (not a clue where to), maybe have some, um, art lessons (could mean anything), settle down to some serious writing (so pretentious), and, er, that sort of thing." My voice tails off.

When it is your turn to be quizzed, dear reader, arm yourself with a respectable list beforehand, so that when the inevitable question pops up, you can shoot from the hip: "Learn classical Urdu, design and print my own wallpaper, make a continuous digital video recording of walking the Pilgrim's Way

(anticlockwise), stand for parliament, breed Russian hamsters." As you pause for breath, your questioner will be silenced also.

There are, of course, inescapable downsides to retirement apart from the obvious one of a drop in income. If, like me, you relied on your secretary to unravel the intricacies of information technology, retirement will be accompanied by a substantial downsizing of communication power, which is inconvenient. Furthermore, the hospital email address, though it may continue for a while, will sooner or later reach a critical point and, like Cinderella's coach, disappear.

Though you may previously have tried to avoid telling strangers you are a doctor, admitting to being retired is worse. Your companion will immediately look carefully at you—a look that says, "I am reassessing your age"—and the conversation is likely to become subtly dumbed down. Rather like the incautious patting of a dog considered too old to bite.

There are also the patients who bullied you into giving them your mobile phone number. The "retirement bush telegraph" never reaches them so they continue to ring at awkward times to tell you that they have a problem. "But I have retired now," you say.

"Oh, sorry to get you out of bed, doc."

"No, retired—not working."

"What?"

"No longer at the hospital."

Pause. "That's alright: I only wanted some advice over the phone—no need for you to go back to the hospital."

Well, I am not going to talk about retirement any more. If anyone asks, I shall say crisply, "I am life retrained," and leave it at that. I feel better now I've got that off my chest. Perhaps I will go and have a cup of tea, a nice hot bath, and then maybe read for a little while. There's a good film on this evening. It finishes quite late, but then, I don't have to get up early in the morning.

Barbara M Southcott *retired consultant oncologist, Chalmington, Dorset*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.