

## The newsletter for people taking part in SEARCH

### Letter from the Editor

Welcome to a new edition of *ReSEARCH*. As you will see, a lot has happened since the last edition, both at the co-ordinating centre in Oxford, and in the field of research that you are participating in.

A new era began for us in Oxford in the summer, and another, extraordinary era ended. In June, the Clinical Trial Service Unit (CTSU), which coordinates *SEARCH*, moved into superb new premises (see page 3), named after Sir Richard Doll, chairman of the independent Data Monitoring Committee of *SEARCH* (see page 3) and one of the world's most famous medical research scientists. And in July, still working hard at the age of nearly 93, Sir Richard died peacefully after a brief spell in hospital. You can learn a little more about this remarkable man

by reading his obituary below.

In addition, Professor Rory Collins, one of the *SEARCH* study coordinators and co-director of CTSU, was appointed, on top of his existing responsibilities, chief executive of UK Biobank. This is an important new nationwide medical research project that will get fully under way in 2006, when it begins to gather information on the health and lifestyle of 500,000 British volunteers aged between 40 and 69. By following this group of people for up to 30 years, doctors and scientists will generate a wealth of new knowledge that will help to improve the prevention, diagnosis and treatment of many common diseases.

As you will see from the Coordinators' letter, although results from other studies on cholesterol lowering have been published recently, the potential of *SEARCH* to help answer vital, unresolved questions remains undiminished. This is why it is so important that as many participants as possible stay in the trial until its completion, now scheduled for the end of 2007. We look forward to keeping in touch with you as we continue towards our goal.

With best wishes

David Simpson, Editor, *ReSEARCH*

### Sir Richard Doll

Sir Richard Doll, one of the world's most distinguished medical research scientists and chairman of the *SEARCH* Data Monitoring Committee, died peacefully in July, aged 92.

While Sir Richard's name is most notably linked to early studies demonstrating the link between tobacco and disease, during his long working life the topics of his research ranged much more widely, including research on asbestos and ionising radiation.

Apart from his work, continuing to just a few weeks before his death, his other interests were equally wide ranging, as a forthcoming biography will describe.

Sir Richard originally intended to be a mathematician, but as he liked to recount, a surfeit of strong college beer before his final scholarship exam at Cambridge left him with a lesser offer than he had hoped for, so he followed his father into medicine.

From the first, in pre-national health service Britain, he was concerned about inadequate health care, housing and other social conditions among the poor. He joined the army medical



William Richard Shaboe Doll  
 28 October 1912 - 24 July 2005.

corps during World War 2, seeing active service in France and Egypt.

Moving to Oxford in 1969, Sir Richard Doll was Regius Professor of Medicine, helped establish the Clinical Trial Service Unit (which

coordinates *SEARCH*), and founded and was first warden of Green College. After retirement he retained an office in the Unit and, until its move earlier this year, could still be seen climbing two flights of stairs to it every day, when not speaking at scientific meetings around the world. Happily, he lived to occupy an office in the Unit's new home, the splendid Richard Doll Building (see p2).

Sir Richard enjoyed a long and happy marriage to Joan, until her death in 2001. He will be missed greatly by innumerable friends and colleagues around the world, for his knowledge and skills, as well as for his eloquence, charm and wit. Above all, colleagues at the Oxford Unit feel the shining example he set in the tone and high standards of research the Unit strives to maintain.

Sir Richard Doll used to say that he wanted to die young as old as possible. That is exactly what he did; and thanks to his life's work, millions of others have the chance of doing the same.

#### Dear Participants

Once again, we would like to thank you very much for your continued participation and commitment to *SEARCH*. Cholesterol-lowering and the use of statins is increasingly in the news, reflecting its fundamental importance to the health of our population. Whilst statins are generally well tolerated, the small risk of adverse effects – which seems to be somewhat greater with the use of higher doses – means that the balance of benefits and risks with the more intensive treatment remains a very important question. Despite 3 recent large studies which compared intensive with standard statin treatment strategies, the jury is still out (for more detail see page 2). The results of *SEARCH* should help resolve this question and provide the evidence which doctors need to decide how widely intensive statin treatment should be recommended.

As you all know by now, we expect *SEARCH* to continue until at least the end of 2007, rather than in 2006 as we anticipated in the last edition of *ReSEARCH*. We have successfully secured additional funding from Merck & Co to extend the average length of follow-up to around 7 years. Merck provides the statins and active and dummy vitamin tablets for *SEARCH*, as well as providing funding via a grant to Oxford University which pays for the clinic nurses and the Oxford

coordinating centre. However, we would like to reassure you that, despite pharmaceutical industry funding, *SEARCH* has been designed by us and is run and monitored entirely independently. Merck has no say in how the study is conducted, or how the money is spent, and all reports of results from the study will be written by us, working with all of the doctors and nurses collaborating on this study in the UK.

The reasons for needing to extend the follow-up of *SEARCH* were explained in our recent letter to you all. To recap, the two main reasons are that fewer than expected numbers of participants have suffered heart attacks, strokes or needed coronary bypass or angioplasty and, secondly, the average difference in cholesterol between those on the higher versus standard simvastatin doses is also somewhat smaller than expected. To make sure that this cholesterol difference is now maintained to the end of the study we need as many as possible of the *SEARCH* participants, like you, to continue the study tablets. Only with enough people continuing their study treatments can we reliably assess which treatment strategy – intensive or standard – is best.

Fortunately, the difference in blood homocysteine between those taking active as opposed to dummy vitamin tablets in *SEARCH* is exactly as expected.

This is thanks to almost 90% of participants continuing their white vitamin or placebo tablets even after several years in the study. However, as explained in more detail on page 3, the results from smaller studies of B vitamins which have looked at heart attacks and strokes have so far been disappointing. *SEARCH* is unique in being large enough, and able to continue long enough, for it to be able to detect reliably the expected benefits of taking these vitamins.

2005 has been an eventful year for CTSU, with a move to new premises on the outskirts of Oxford, and the final two years of *SEARCH* promises to be equally busy. We are fortunate to have a large number of highly skilled and dedicated nurses and receptionists working in local study centres across the UK, and an excellent team of administrators, laboratory technicians and support staff here in Oxford, who ensure that *SEARCH* runs smoothly and efficiently. Your on-going support of the study is greatly appreciated by us all, and we wish you a very happy and healthy 2006!

   
 Rory Collins Jane Armitage  
 SEARCH Study Coordinators

## Double Blind Trials and the Data Monitoring Committee

As a **SEARCH** volunteer, if you take all 3 pills each day, you are certainly receiving simvastatin (either 20mg or 80mg) to lower your cholesterol and, in addition, either folic acid and vitamin B<sub>12</sub> or a dummy pill. The **SEARCH** study is "double blind". This means that neither the trial staff (based at your local hospital or in Oxford) nor trial participants (like you) know which of the possible treatments are being used by particular people. This "double blind" design is very important as it helps ensure the integrity of the study and reduces the chance of participants or medical staff falsely assuming that the allotted study medication is responsible for benefits or side effects ("bias").

When **SEARCH** started over 5 years ago it was not clear whether people who have had a heart attack should have their cholesterol lowered as much as possible with a high dose statin, or if a normal dose of statin was adequate.

Despite recent results from other studies (see p3), this still remains unclear.

Because **SEARCH** is "double blind", for the time being the trial coordinators in Oxford do not know whether one treatment is better (or worse) than another. Only at the very end of the study, when we "break the code" and unblind individual **SEARCH** participants' allocation, will we be able to determine which treatment is best.

However, there is an independent Data Monitoring Committee which meets regularly and has access to the "unblinded" results of the trial. This committee was chaired by Sir Richard Doll until his death in July 2005 and this role has now been assumed by Professor Lars Wilhelmsen, an eminent Swedish doctor who had been the deputy chair. On the basis of the most up to date results of **SEARCH** and findings from similar studies that are conducted elsewhere, this committee has the important task of

deciding whether one treatment has been shown clearly to be better than the other. If they believe that this is the case, they have the responsibility to tell the study coordinators who can then stop **SEARCH** and inform participants; otherwise, the study will run its scheduled course.

The Data Monitoring Committee last met in March 2005 and Prof Wilhelmsen has reviewed **SEARCH** more recently. Following careful consideration of the results from **SEARCH** available to them, and other relevant study results (see p3), they felt that it was currently both appropriate and important for **SEARCH** to continue for a further 2-3 years. This extension of **SEARCH** should allow a clear answer to emerge about whether high dose statins are better than normal dose statins, and whether folic acid and vitamin B<sub>12</sub> prevents heart disease. Your continued participation in the study is very valuable.



### We Have Moved!

Our postal address has changed:

SEARCH  
Clinical Trial Service Unit  
Richard Doll Building  
University of Oxford  
Old Road Campus  
Roosevelt Drive  
Oxford OX3 7LF



Our phone number (Freefone 0800 585323) and e-mail address ([search@ctsu.ox.ac.uk](mailto:search@ctsu.ox.ac.uk)) remain unchanged

## What about 'B' vitamins?

– *Results from the Norwegian NORVIT Study*

In addition to the two pink / tan coloured tablets (which are either 20mg or 80mg simvastatin) most patients in **SEARCH** take one round white pill each day as well. This white pill is either folic acid and vitamin B<sub>12</sub> or a dummy pill. Folic acid and vitamin B<sub>12</sub> lowers levels of homocysteine in the blood. High levels of homocysteine (a protein related waste product) have been linked to increased risk of heart attacks and stroke and, therefore, lowering the level of this chemical in the blood may help prevent these problems.

A Norwegian study investigating the effects of lowering homocysteine with B vitamins (folic acid and vitamin B<sub>12</sub>, which we are using in **SEARCH**, along

with vitamin B<sub>6</sub>) has recently finished, and the results have been presented at an international conference in Stockholm. This study, called NORVIT, involved around three and a half thousand Norwegian men and women who (like **SEARCH** participants) had had a heart attack. They took either a mixture of B vitamins or dummy pills for around three and a half years.

In that study, taking folic acid and vitamin B<sub>12</sub> did not appear to make any difference to the numbers of heart attacks and strokes in this group of patients (nor did taking vitamin B<sub>6</sub>). It is possible, however, that this study was both too small and too short to be able to detect a small but worthwhile benefit of these vitamins.

**SEARCH** has over 12,000 participants who are randomised to receive either vitamin supplements or dummy tablets for around 7 years. Because **SEARCH** is over three times larger than NORVIT, and its duration twice as long, it should have a very much better chance of detecting reliably whether using these B vitamins to lower homocysteine reduces the risk of heart attacks and strokes. By continuing to take your **SEARCH** study medication you are participating in one of the largest studies of homocysteine lowering in the world, the results of which may help improve the care of patients with heart disease in future years.

# High Dose Statin Treatment or Not?

## – Results of “A to Z”, “TNT” and “IDEAL”

Whilst it is now clear that people who are at an increased risk of heart disease benefit from statin therapy to lower cholesterol, it remains unclear whether they should be treated with high or normal dose statins.

**SEARCH** participants receive simvastatin at a daily dose of either 80mg or 20mg. Over the course of the study we will explore the balance of benefits and side effects of these two doses.

**SEARCH** is one of a number of large scale clinical trials investigating the role of more intensive cholesterol lowering to prevent heart disease. Doctors around the world remain undecided about the best way of managing such patients. Since the last edition of *ReSEARCH* in Autumn 2004, three studies have explored this question further with results that you may find interesting.

One study, called “A to Z”, involved over 4000 patients who were admitted to hospital with suspected heart attacks. After an initial phase of standard dose or dummy treatment they were given either normal or high dose simvastatin (the same drug that is being used in **SEARCH**). Patients were seen in clinic for the following 2 years and, at the end of the study, there was no clear evidence that one treatment was better than the other. Patients treated with high dose simvastatin seemed to have somewhat fewer heart attacks and strokes, but an increased

level of side effects, compared to the standard dose. However, this study was too small and its duration too short to rule out the possibility that these small differences were due to chance.

The other two studies have compared high dose atorvastatin (another cholesterol lowering drug similar to simvastatin) with a standard statin regimen. In “Treating to New Targets (TNT)”, over 10 000 volunteers who had survived a heart problem were recruited and, after around 5 years of

treatment, those treated with high dose atorvastatin had fewer heart problems than those on a usual dose of atorvastatin. In “IDEAL”, which has recently been published, just under 9000 patients who had had a previous heart attack were given either high dose atorvastatin or usual dose simvastatin for around 5 years. High dose atorvastatin appeared to prevent more heart problems than usual dose simvastatin but this difference was not “statistically significant”, leaving open the possibility that it could have arisen by chance. In both studies, those on high dose atorvastatin had higher rates of abnormal liver function blood tests detected at routine follow-up appointments, but this was not reported to have led to any particular illnesses.

When considered together, these recent studies suggest that intensive cholesterol lowering may well reduce the risk of further heart disease, but the balance of benefits versus risks with this approach is uncertain. The independent Data Monitoring Committee of **SEARCH** (see p3) has carefully considered the results of the two earlier trials (“A to Z” and “TNT”), along with the **SEARCH** results, and has concluded that it is both appropriate and necessary for the study to continue. The medical community eagerly awaits the results of **SEARCH** to help provide a clear answer as to whether patients with heart disease should be on high or normal dose statins to prevent further vascular disease.

### Want more information?

*The results of “A to Z” and “IDEAL” trials were published in the Journal of the American Medical Association, and “TNT” appeared in The New England Journal of Medicine. (see below).*

*Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004 Sep 15;292(11):1307-16*

*High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005 Nov 16;294(19):2437-45*

*Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005 Apr 7;352(14):1425-35*

We are accustomed to moving **SEARCH** participants’ appointments around to accommodate the many professional and social commitments they have. It came as a surprise, however, when Michael Roberts, a retired civil engineer from Ruthin, North Wales, informed us that he would be unable to keep an appointment as he would be climbing a mountain!

Just over 10 years ago Mr Roberts had a heart attack. It was not long, however, before he was out and about in the North Wales countryside. A keen walker, he marked the second anniversary of his heart attack by climbing Tryfan, a mountain that rises to over 3000 feet above sea level and is one of the most famous peaks in



Snowdonia - raising funds for the British Heart Foundation through sponsorship of the event.

Mr Roberts’ interest and enthusiasm for hiking, hill climbing and gentle mountaineering have persisted over the years, and he decided this year that a repeat of his ascent of Tryfan would be a fitting way of “celebrating” the 10th anniversary of his heart attack.

With the help of a like-minded friend, our youthful 75 year old undertook a rigorous training programme to ensure he was in tip-top condition to complete the climb. The next time Mr Roberts phoned us, it was from the breezy heights of the Welsh peak. Happy anniversary!

## **HELP!** – My doctor wants to prescribe a statin.....

In **SEARCH**, participants who take one tan-coloured round pill and one dark pink capsule-shaped pill each day are definitely receiving simvastatin (to lower cholesterol) at a daily dose of either 20mg or 80mg.

The benefits of statins in patients, who (like all **SEARCH** volunteers) have had a previous heart attack, are clear. Occasionally, doctors or practice nurses running heart disease prevention clinics prescribe statins to **SEARCH** participants who are already receiving simvastatin in the study. This is potentially harmful as it may increase the statin dose too much.

So, if you are taking 3 **SEARCH** pills daily, what should you do if your doctor or practice nurse tries to prescribe a statin?

- 1 Remind them that you are a **SEARCH** participant (we have written to all volunteers’ GPs at the start of the study).
- 2 Suggest that they discuss any concerns about your cholesterol level and drug treatment with the **SEARCH** study doctors in Oxford on Freephone 0800 585323
- 3 If they are sure that they wish to take charge of your cholesterol lowering medication, please stop the pink and tan coloured **SEARCH** pills, but please remember to tell the coordinating

centre of this change via the Freephone number. You can safely continue the round white tablets, which contain either active vitamins or dummy.

- 4 It is very important that we remain in contact with you (even if you have stopped study medication), and we would be pleased if you continued attending clinics even if you no longer take **SEARCH** pills.

We hope that as many **SEARCH** volunteers as possible remain in the trial and on all their study medications. This will help to ensure that the results we obtain from the study are reliable and relevant to people with heart disease worldwide.

# Carnival of the Animals

Visit the homes of **SEARCH** volunteers around the country and there is a good chance you will find a pet animal or two. Often it will be a mere cat; but if you had dropped in to see Roy Bedford of Wakefield, over the past few years, you might have found - a meerkat. Or a quick, inquisitive, mischievous group of them even. Or squirrels, swans, ducklings, a tawny owl or even Gordon the Canada goose. For Roy, 75, has found himself keeping a wildlife rehabilitation centre in his back garden and in borrowed quarters at a friend's farm.

It all started when Roy spotted a sick cygnet with a swelling in its neck among the swans he used to feed while walking his dog. After catching it, a vet found it had swallowed a hook and fishing line, which he removed, saving the life of the cygnet. It became the first of many birds and animals nursed back to health by Roy and his family, before being released back into an appropriate habitat.



Roy meanwhile attended training courses to learn how to handle and look after his new charges. Sometimes a creature is brought in after falling from its nest, like the squirrel that went on to star in the recent remake of *Willie Wonka and the Chocolate Factory*. Or someone realises too late that animals that are naturally wild, like meerkats, are simply unsuitable as pets.

Roy never intended such a role in life. From joining the army as a 'boy soldier' at the end of the second world war, he enjoyed a long career in band music. First as a regimental bandsman for nearly thirty years, for many of them as bandmaster, he then moved to Northern Ireland to become director of music for the Royal Ulster Constabulary. Roy and his family loved the life there, though the accumulated sadness of organising music for around a hundred and fifty funerals during the troubles was one of the factors leading to their decision to return home to Yorkshire. Now the family is so well known for the service they provide to animals that plans are being made to put the whole thing on a proper footing. His daughter Jennifer is setting up a centre in a new home and garden acquired for the purpose. Roy and his wife will have the satisfaction of having started something very worthwhile, while having more free time to enjoy their retirement. And no more beady eyes on Roy's study treatment.

## Safety reminder: Some tablets increase the risk of muscle problems

Very rarely, statins can cause unexplained muscle pain or weakness, which is called 'myopathy' when it is accompanied by a significant increase in the muscle blood test called 'creatin kinase' (or, for short, 'CK'). That is why volunteers in **SEARCH** are asked to report any new or unexplained muscle pain at each clinic visit, and a blood sample is taken to measure CK levels in the blood. Some other treatments can increase the risk of myopathy

when taken with simvastatin or other statins. These are listed in the boxes below. So, if any of these medications are started by **SEARCH** participants, we recommend either that the study simvastatin tablets are stopped (when the risk may be substantially increased: Box 1), or that the study simvastatin tablets are continued with care (when the increase in risk is smaller: Box 2). Some UK pharmacies buy their drug supplies from outside the

UK, in which case drug names may differ from those listed. If you are in any doubt about whether your **SEARCH** tablets react with any of your other medication, please ring the Freefone service (0800 – 585323) to check with one of the study doctors. **In all cases, however, any unusual or unexplained muscle pain or weakness should be reported via the Freefone number as soon as possible.**

### Box 1: Drugs that can increase the risk of myopathy substantially, and so should NOT be taken with the study simvastatin tablets

#### For kidney and heart transplants:

- **Ciclosporin** (Neoral, Sandimmun, SangCya)

#### For heart irregularities (arrhythmias):

- **Amiodarone** (Cordarone, Cordarone X, Amidox)

#### For lowering cholesterol:

- Non-study statins: **Simvastatin** (Zocor, Zocor Heart-Pro, Simvador, Ranzolont, Simzal, Simlup, Lipex, Inegy)  
**Atorvastatin** (Lipitor, Atorlip)  
**Fluvastatin** (Lescol)  
**Pravastatin** (Lipostat, Eptastatin, Pravachol)  
**Rosuvastatin** (Crestor)
- "Fibrates": **Bezafibrate** (Bezalip, Bezalip Mono, Bezagen XL, Liparol XL, Zimbacol XL)  
**Ciprofibrate** (Modalim)  
**Fenofibrate** (Lipantil, Lipantil Micro, Supralip)  
Fenogal  
**Gemfibrozil** (Lopid)
- High dose niacin: **Nicotinic acid** (Niaspan) more than 1 gram/day  
**Acipimox** (Olbetam)

**If you are prescribed any of these treatments, you should stop the study simvastatin tablets (the tan-coloured round ones and the dark pink capsule-shaped ones) and contact your study nurse (or ring the Freefone service on 0800-585323) for further assistance.**

### Box 2: Drugs that can increase the risk of myopathy to a lesser extent, and so may be continued with study simvastatin tablets (but with increased vigilance about muscle symptoms)

#### For some irregularities of heart rhythm (arrhythmias):

- **Verapamil:** (Berkatens, Cordilox, Securon, Univer, Tarka, Verapress, Vertab, Zolvera, Ethimil, Ranvera, Vera-til, Geangin, Hypaneze)

#### For infections:

- **Erythromycin:** (also sold as Arpimycin, Erycen, Erymax, Erymin, Erythrocin, Erythroped A, Erythrolar, Erythromid, Kerymax, Tiloryth, Ilosone, Ilotycin, Retcin, Rommix)
- **Clarithromycin:** (Klaricid, Helimet, Heliclear)
- **Telithromycin:** (Ketek)

#### For fungal infections (only if these drugs are given by mouth or injection, ointments or lotions are fine to use):

- **Itraconazole** (Sporanox)
- **Ketoconazole:** (Nizoral)
- **Miconazole:** (Daktarin)

**If you are prescribed any of these drugs then continue to take your study treatment (unless advised otherwise), but contact your study nurse (or ring the Freefone service on 0800 585323) for further advice.** Sometimes this advice will involve an extra clinic visit to measure CK levels in the blood. In other cases, for example with certain short courses of antibiotics, you may be advised to stop the study simvastatin temporarily until the other treatment has been completed.

The study vitamins are not known to cause any adverse effects when taken with any other treatments. Folic acid can, however, disturb the effects of methotrexate (given

for severe arthritis or psoriasis, and for some other conditions) which works by interfering with the body's handling of folic acid. So, if you are prescribed methotrexate you should

stop the white study tablets (which contain folic acid or dummy) and contact the study nurse (or ring the Freefone service on 0800-585323) for further assistance.