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

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 completion now scheduled for the end of 2007, we would like to thank you very much for your continued participation and commitment to SEARCH.

Welcome to a new edition of SEARCH. 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.

Sir Richard Doll

William Richard Shaboe Doll

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, SEARCH

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!
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 (Freephone 0800 585323) and e-mail address (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 B12, or a dummy pill. Folic acid and vitamin B12 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 B12) which we are using in SEARCH, along with vitamin B12 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 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 B12 did not appear to make any difference to the numbers of heart attacks and strokes in this group of patients (nor did taking vitamin B12). 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 illneses.

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 p31) 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.

ReSEARCH

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.
Drugs that can increase the risk of myopathy

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid</td>
<td><strong>Ciclosporin</strong> (Neoral, Sandimmun, SangCya)</td>
</tr>
<tr>
<td>Heart conditions</td>
<td><strong>Amiodarone</strong> (Cordaron, Cordaron X, Amidox)</td>
</tr>
<tr>
<td>Lowering cholesterol</td>
<td><strong>Simvastatin</strong> (Zocor, Zocor Heart-Pro, Simward, Ranzolont, Simzal, Simulp, Lipex, Inegy) for non-study statins. <strong>Atorvastatin</strong> (Lipitor, Atorlip) <strong>Fluvastatin</strong> (Lescol) <strong>Pravastatin</strong> (Lipostat, Eptastatin, Pravachol) <strong>Rosuvastatin</strong> (Crestor) <strong>“Fibrates”</strong>: <strong>Bezafibrate</strong> (Bezalip, Bezalip Mono, Bezagen XL, Liparon XL, Zimbalcol XL) <strong>Ciprofibrate</strong> (Modalim) <strong>Fenofibrate</strong> (Lipantil, Lipantil Micro, Supralip) <strong>Gemfibrozil</strong> (Lopid) <strong>High dose niacin</strong>: <strong>Nicotinic acid</strong> (Niaspan) more than 1 gram/day <strong>Acipimox</strong> (Olibetam)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>For kidney and heart transplants</td>
<td><strong>Ciclosporin</strong> (Neoral, Sandimmun, SangCya)</td>
</tr>
<tr>
<td>For heart irregularities</td>
<td><strong>Amiodarone</strong> (Cordaron, Cordaron X, Amidox)</td>
</tr>
<tr>
<td>For infections</td>
<td><strong>Erythromycin</strong> (also sold as Arpimycin, Erycen, Erymax, Erynin, Erythrocin, Erythroid A, Erythrob, Erythromycin, Ketek, Tesoryl, Tesoryl B, Zinacin) <strong>Clarithromycin</strong> (Klaricid, Helicid, Heliclear) <strong>Telithromycin</strong> (Ketek)</td>
</tr>
<tr>
<td>For fungal infections</td>
<td><strong>Itraconazole</strong> (Sporanox) <strong>Ketoconazole</strong> (Nizoral) <strong>Micronazole</strong> (Daktarin)</td>
</tr>
</tbody>
</table>

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.