

Sequencing of *Helicobacter pylori* will radically alter research

Hilary Bower, London

Publication of the complete genome sequence of the gut pathogen *Helicobacter pylori* will radically change research approaches and pave the way for completely new methods of treatment, say molecular experts.

Scientists from the Institute for Genome Research in Rockville, Maryland, United States, have described how *H pylori* has a circular genome consisting of 1667 867 base pairs (*Nature* 1997;388:539-47). The sequencing offers important clues about how the bacterium, which is the main non-pharmaceutical cause of ulcers, manages to survive and thrive in the hostile acidic environment of the human stomach.

H pylori is only the seventh bacterium to be completely sequenced. Publication of the sequence places the information in the public domain and ends the simmering controversy over the actions of two major pharmaceutical companies, which have each bought almost complete versions of the sequence, reputedly for a price of around £15m (\$24m), but disallowed public access.

Dr John Atherton, a molecular geneticist funded by the Medical Research Council and a gastroenterologist at University Hospital, Nottingham, hailed the

genome sequence as "dynamite." "This is the biggest thing to happen in years. It is very, very exciting. It will completely change the way we do research on *H pylori*, speeding it up immensely. It will probably halve the time it now takes to track links between bacterial structures and enzymes and the genes that encode them," he said. "It also gives us an enormous list of genes present in *H pylori*—two thirds of which are similar to genes found in other bacteria—and it gives us an overall picture of how *H pylori* functions so we can put individual bits of research into their wider context."

Roy Pounder, professor of medicine at the Royal Free Hospital, London, and a trustee of the British Digestive Foundation, said that therapeutically the genome offered a new range of enzymes and proteins as treatment targets. But he questioned whether such targets would be commercially viable because of the multiple strains of *H pylori* and their ability to change subtly in individual people. However, Dr Atherton believes that the sequence will shift the whole search for therapeutic agents on to new ground. "Treatment has become more effective in recent years, but antibiotic resistance is an increasing problem and there



Helicobacter pylori is only the seventh bacterium to be sequenced

is enormous interest in finding treatments that aren't dependent on antibiotics. The information contained in the genome offers a large number of other routes. For example, the sequence shows glucose is the only source of carbohydrate. As it's almost inconceivable that other strains would have a different energy source, if you could block its use of glucose, you could kill any strain."

The genome, with its clues to the complex mechanisms that *H pylori* uses to fool the human immune system—not just temporarily but often over a lifetime—also opens doors for investigating possible vaccine

targets. And it may shed light on the puzzle of *H pylori* toxicity and why some strains cause ulcers while others do not. Finally, says Dr Atherton, the sequence will fascinate bacteriologists: "It's always been thought that bacteria evolve slowly like other organisms, but it looks as though *H pylori* has evolved in a completely different way—acquiring genes from a whole range of bacterial and possibly even non-bacterial sources. It also looks like it has genes that have adapted to mimic human genes, which may explain why this pathogen manages to evade the immune system so effectively." □

Gene mutation offers resistance to AIDS

Jacqui Wise, BMJ

People who are infected with HIV-1 yet do not develop AIDS for up to 20 years may be protected by a genetic mutation, according to a genetic analysis

of 3000 patients with AIDS.

American researchers have identified a mutation in a chemokine receptor gene, CCR2, that delays the progression of AIDS by several years (*Science* 1997;277:959-64). Patients with the CCR2 mutation progressed to AIDS at least 2-4 years later than individuals carrying the normal gene.

Genetic association analysis of five AIDS cohorts totalling 3003 patients showed that

although the CCR2 mutation does not protect against getting infected with HIV-1, it does offer protection for individuals already infected with the virus.

This latest research complements earlier studies showing that a mutation in the CCR5 chemokine receptor is associated with survival. The authors noted that the protective effect of CCR2 is of a similar magnitude to and separate from the protection observed by CCR5 muta-

tions. They said that the survival of about a quarter of people with long term HIV infection who avoided AIDS for more than 16 years can be attributed to their CCR2/CCR5 genotype.

However, CCR2 does not protect against HIV-1 infection, whereas CCR5 cells are strongly resistant to infection. Also, the CCR5 mutation is unique to white people, whereas the CCR2 mutation was found in every ethnic group tested. □

In brief**University to investigate**

research fraud: The University of Glasgow has set up a panel to examine research conducted by Professor Peter Behan. Professor Behan was accused of "cooking" the results of research linking the chronic fatigue syndrome to organophosphates (2 August, p 271). His case is awaiting judgment in the High Court. The examining panel will include a senior professor, a lawyer, a statistician, and a clinician.

Mixed sex wards to go:

The Department of Health aims to get rid of mixed sex accommodation in hospitals in England within two years. This will require some health authorities to revise their existing targets of three to five years, which health minister Baroness Jay said were unacceptable.

Dutch court denies sickness benefit to patient with "ME":

The Netherlands' highest social security court has denied benefit to a 34 year old patient with the chronic fatigue syndrome because no physical or mental causes of the illness could be objectively identified. Doctors have called for clarification about such patients' entitlement to sickness benefit.

Breaches of tobacco advertising agreement doubles in year:

The number of breaches of the voluntary agreement to restrict tobacco advertising in Britain doubled last year, according to a report from the watchdog Committee for Monitoring Agreements on Tobacco Advertising and Sponsorship. Of the 30 direct breaches of the agreement, 19 were related to poster sites near schools.

More research needed on

marijuana: The United States' National Institutes of Health have released an expert panel report which concludes that, as there is a dearth of evidence, clinical trials are needed to look into the efficacy of marijuana as an analgesic, appetite stimulant, and antiemetic. The panel calls for the development of "smoke free inhalation delivery systems" to deliver the active ingredients in marijuana.

United States bans smoking on federal property

Terri Rutter, *Boston*

The president of the United States, Bill Clinton, has declared a ban on smoking in all federal buildings, but he has backtracked on his plan to prohibit smoking around building entrances and courtyards.

"Cigarette smoking is the most single significant public health problem facing our people today," Mr Clinton said as he announced his order for smoke free buildings within a year.

A draft of the executive order, which received extensive media publicity last week, would have banned all smoking within 15 m (50 feet) of federal buildings, even if the area encompassed a public pavement. Administration officials said that such a provision would be "going too far" in one step, but the order gives individual agency heads the discretion to "evaluate the need" for an outdoor ban.

Excluded from the ban are

buildings that the president does not have complete control over, including congress and the courts. It is expected that many government offices will follow the president's example and

impose their own smoking bans.

Currently, federal office buildings have separate rules about smoking and these vary greatly. The Pentagon, the Department of Health and Human Services, the postal service, and the Environmental Protection Agency already have bans in place. Smoking is permitted in buildings at other branches of the federal government, although only in restricted areas. □



People who smoke outside buildings in the US have won a reprieve

Britain has become less equal in death

Jacqui Wise, *BMJ*

If you live in Glasgow you are 66% more likely to die prematurely than if you live in rural Dorset and 31% more likely than if you live in Bristol. Where you live in Britain is a better guide to your chance of an early death now than at any time in almost half a century, according to a report from the Joseph Rowntree Foundation.

Although absolute mortality for all groups in society has fallen steadily since the 1950s, the gap between people living in different areas has widened, particularly since the 1980s. People living in the tenth of areas with the highest death rates are now almost twice as likely to die prematurely as those who live in the tenth of areas where the rates are lowest.

The analysis of the statistics, by Dr Daniel Dorling of the University of Bristol's department of geography, shows that

those living in the worst tenth of areas in terms of mortality are in those areas where indicators of poverty are also the greatest. One in 12 of the population of Britain now live in areas where the standardised premature death rates are more than 15% above the national average.

The study found that despite a dramatic and continuing decline in death rates among babies under 12 months since the 1950s, variations between areas are increasing. A girl born in Leeds, for example, is more than twice as likely to die within the first year of life than a girl born in a Dorset town. Mortality in the first year of life for boys born in Blackburn, Halifax, and Preston has risen against the national trend since 1981 and is now nearly double the average level.

And although the number of children who die between ages 1 year and 14 years is very small, differences between areas can still be dramatic. For example, proportionally eight times as many boys aged 1 year to 4 years died in Manchester between 1990 and 1992 as died in rural Gloucestershire.

Dr Dorling said he did not know why the differences have become so pronounced. "However, it does seem that the trend has occurred too quickly—and involves too many deaths—to be explained simply by a changing distribution of wealth, changing causes of death, or as a reflection of past health inequalities."

The report concludes that it is unlikely that Britain will be able to meet its commitment to a 25% reduction in health inequalities by the year 2000. The British government says that it is committed to reducing inequalities in health, with proposals due out in the autumn. Commenting on the report, the health secretary, Frank Dobson, said: "Inequality in health is the worst inequality of all. There is no more serious inequality than knowing that you will die sooner because you are badly off." □

Death in Britain: How Local Mortality Rates have Changed: 1950s to 1990s can be obtained from York Publishing Services, 64 Hallfield Road, Layerthorpe, York YO3 7XQ, price £13.45. A summary can be found on the Joseph Rowntree Foundation's web site (www.jrf.org.uk).

French scientist resigns in nuclear contamination row

Alexander Dorozynski, Paris

Professor Charles Souleau, the president of a committee appointed by the French government to evaluate the risk of contamination by the La Hague nuclear reprocessing plant in Normandy, resigned last week after a public disagreement with the rest of the committee. The row came to a head when Professor Souleau presented reassuring figures on exposure doses to the public which, it transpired, had been produced by the state nuclear company Cogema, which runs the La Hague plant.

Professor Jean-François Viel, a French epidemiologist, first established a causal link between the incidence of leukaemia and low doses of radiation near the plant in a study published in the *BMJ* in January (1997;14:101-6).

The research was initially dis-

paraged by several official bodies, but Corinne Lepage, then minister of the environment, asked for an independent evaluation of the risks and appointed Professor Souleau, dean of the faculty of pharmacy of Châte-nay-Malabry near Paris and president of the environmental section of France's Superior Council of Public Hygiene, to head the scientific committee.

In June the committee confirmed the "seriousness and coherence" of Professor Viel's original study, and an independent study commissioned by Greenpeace showed the existence of radioactive sediment near a pipe carrying waste material from the La Hague plant (28 June, p 1854).

Professor Souleau disagreed and a few days later presented

reassuring data on exposure doses at a public meeting in Normandy. However, it appears that these data had not been seen by his committee but had been issued by Cogema.

On 10 July Dominique Voynet, the new minister of the environment, banned fishing and water sports near the La Hague plant's outlet, and last week Professor Souleau, announcing his resignation, sent members of the scientific committee an unusually virulent and emotional letter. In the letter he describes Greenpeace activists as "totalitarians," preparing the world for "a gigantic collective suicide."

He also accuses the "anglo-phone (scientific) press lobby" of imperialism. "This lobby ... makes and breaks reputations, careers, and myths," he wrote in a letter to committee members. "To the question everybody poses: has Professor Viel been manipulated? I answer 'yes.'" Professor Souleau wrote to the *BMJ* in July saying that his committee had

not validated the conclusions of Professor Viel (26 July, p 254).

According to another committee member, interviewed by *Le Monde* newspaper, Professor Souleau had great psychological difficulties in reconciling his personal convictions with the committee's work. "It's hard to think he deliberately chose to lie by presenting Cogema documents as being the results of his group's work; rather, he was marked by very strong convictions which, at first, he sought to neutralise." Ms Lepage said his statements were totally incompatible with the independence needed in order to head up the scientific commission.

The study of the impact of nuclear contamination on the environment in Normandy will continue, and its scope may be widened to include other nuclear sites. Professor Alfred Spira of the National Institute of Health and Medical Research (INSERM), a specialist in public health and epidemiology, is expected to head it. □

Genetic engineering reverses antibiotic resistance

Kamran Abbasi, *BMJ*

Researchers have developed a genetic engineering technique that for the first time allows drug resistant bacteria to be rendered drug sensitive. This may prove to be a cheaper method of negating antibiotic resistance than the current approach of developing new drugs.

A team of biologists from Yale University in the United States, led by Nobel prize winner Professor Sidney Altman, has used plasmids that contain synthetic genes coding for small oligoribonucleotides, called external guide sequences (EGSs), to infiltrate drug resistant strains of *Escherichia coli* (*Proceedings of the National Academy of Science* 1997;94:8468-72).

Once inside, the external guide sequences facilitate the cleavage and inactivation of messenger RNA associated with the bacteria's drug resistant genes. In this way the bacteria are transformed from drug resistant to drug sensitive. In this study the bacteria were originally resistant to chloram-

phenicol and ampicillin, but the technique should be just as effective for bacteria resistant to other antibiotics.

Professor Altman said: "This is a different approach to antibiotic resistance from the usual pharmaceutical company approach. It takes a shorter time and is less expensive. In a couple of months we can develop EGSs against particular genes."

Furthermore, the researchers showed that increasing the external guide sequences to messenger RNA ratio and targeting more sites on the messenger RNA both resulted in a higher success rate in eliminating drug resistance.

Antibiotic resistance has become an increasing clinical problem in the past 15 years, leading to the use of more expensive antibiotics that often have more side effects. Notably, the eradication of tuberculosis has been complicated by the rise in drug resistant strains of *Mycobacterium tuberculosis*. Antibiotic resistance is also a problem



HANK HODGSON/ISTE

Antibiotic resistance has become an increasing problem

in the treatment of *Haemophilus influenzae*, a common vector in childhood meningitis, epiglottitis, and pneumonia.

Professor Altman won the 1989 Nobel prize for his discovery that RNA, as well as being a carrier of genetic material, can be involved in chemical reactions. He has been working on the problem of bacterial drug resistance for the past six years.

Although the Yale team has shown the success of their technique in laboratory cultures, it readily admits that it will be sev-

eral years before a therapeutic tool is developed. The question now is whether the development of this technique will indeed prove cheaper and more practical than the present strategy of developing new antibiotics.

Professor Altman added: "I want to emphasise that this is purely laboratory work at present, and further research will be needed in animal models, and, after that, humans. We will continue to refine the technique but cannot afford to take the research further ourselves." □

Death rates in Russia rise dramatically

Jacqui Wise, *BMJ*

Russia has seen a huge rise in death rates since the collapse of the Soviet Union in 1991. The biggest rise has been among deaths related to alcohol and as a result of accidents and violence.

Between 1984 and 1987 life expectancy at birth increased from 61.7 to 64.9 years in men and from 73.0 to 74.3 years in women. But between 1987 and 1994 life expectancy fell to just 57.6 years in men and 71 years in women.

Researchers from the London School of Hygiene and Tropical Medicine and the Centre of Demography and Human Ecology in Moscow found that except for neoplasms all major causes of death declined between 1984 and 1987 and increased between 1987 and 1994 (*Lancet* 1997;350:383-8).

The authors say: "The magnitude and steepness of the fluctuations in mortality rates and life expectancy reported here for Russia are without parallel in the modern era, with the exception of some other parts of the former Soviet Union."

In absolute terms men have been most affected by the recent fluctuations in mortality, but in relative terms women have been affected to almost the same degree as men, even for deaths from accidents and violence and causes related to alcohol. The mortality trends were strongest among young adults and middle aged people. Death rates among elderly and young people, who are usually perceived to be the most vulnerable, seemed not to

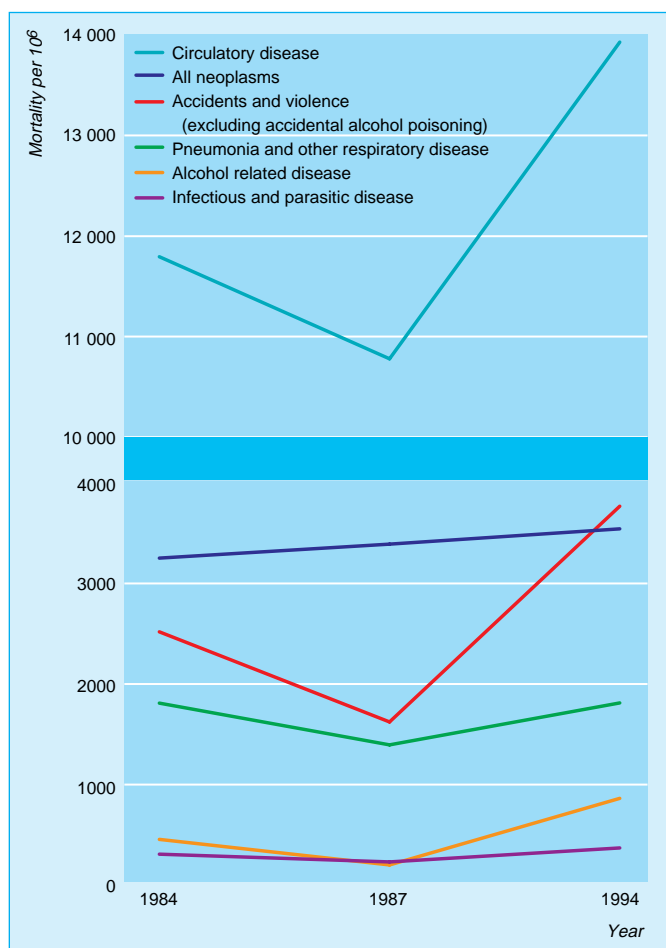
be greatly affected by events between 1984 and 1994.

The largest declines and subsequent increases in proportional terms were seen for deaths related to alcohol and deaths from accidents and violence (see figure). However, pronounced effects were also seen for deaths from infections, circulatory disease, and respiratory disease. Such variations are unlikely to be an artefact because of the stability of mortality from neoplasms over the whole period.

The authors say that extremely high alcohol consumption, together with the habit of binge drinking, may be resulting in a large number of deaths from circulatory disease in middle age, mainly from arrhythmias or cardiomyopathies.

Consumption of alcohol started to decline in 1984 and fell even more rapidly with the introduction of President Gorbachev's antialcohol campaign in 1985. However, state restrictions on the supply and sale of alcohol led to an increase in home brewing at the end of the 1980s. This trend continued into the 1990s, when sales of alcohol increased again as the political will to restrict consumption faded and the relative price of alcohol fell. Increases in real wages between 1992 and 1994 led to further increases in alcohol sales.

In 1987 accidental poisoning by alcohol accounted for over 80% of deaths among men under 45. The consumption of pure alcohol per head in Russia in 1993 was 14.5 litres of pure



Between 1984 and 1994 mortality for Russian men declined and then increased for all major causes of death except neoplasms

alcohol a year, or 40 g of pure alcohol a day. A survey carried out in 1992 and 1993 showed that 82% of Russian men consumed alcoholic drinks.

In an accompanying editorial Daan Kromhout and colleagues from the National Institute of Public Health and the Environment in Bilthoven, Netherlands, say that this high intake of alcohol in conjunction with a diet low in vegetables and fruits and

with high smoking rates could account for the high death rates from cardiovascular disease. They say: "The appalling life expectancies in Russia ... can soon be improved by measures such as preventing alcohol abuse, discouraging smoking, and encouraging a healthy diet. To make any impact these measures should be included in the socioeconomic reform now taking place in Russia." □

Road injury fees to be enforced in Britain

John Warden,
parliamentary correspondent, BMJ

A fee of £21.30 (\$34) payable to the first doctor who attends a person who has been hurt in a road accident is likely to be scrapped in a forthcoming review of how the NHS is

reimbursed for treating such patients.

It was announced in the budget last month that hospitals will be expected to recoup from insurers the full fees—up to about £3000 a case—for patients hurt in road accidents. This principle was first established in the 1930s but is applied erratically.

The government is now considering new legislation to ensure that the NHS recovers the full £150m estimated to be available under the rules.

The charges legally fall on the guilty party in any accident and should be covered by insurance.

There is a flat fee of £21.30 in all cases to cover the first emergency treatment. Subsequent fees are up to £2949 for inpatient care or a maximum of £295 for outpatient treatment. As a concession to persuade insurance companies not to raise motorists' premiums, the government is proposing to waive the £21.30 flat fee.

Some insurers have said that

premiums would have to rise by between £10 and £20 to cover the extra costs of full reimbursement. But the Association of British Insurers said that most companies already take their liability under the existing law into account when assessing premiums.

Only about half of hospital trusts attempt to reclaim their costs, and total annual receipts are believed to be about £20m. As the law stands, trusts have discretion to levy the fee. This may be removed in future. □

Health of heroin misusers in Germany drops

Helmut L. Karcher, *Munich*

The general health of heroin misusers in Germany has become much worse in recent years, according to a study of more than 1000 misusers.

Researchers studied 1041 opiate misusers participating in a detoxification programme at the psychiatric hospital in the University of Hamburg between 1989 and 1993. The average opiate treatment index score—developed to provide a scale for estimating the health of opiate misusers—rose from 2.8 to 3.2 between the two periods (*Fortschritte der Medizin* 1997;115:41-5). Such a rise indicates a considerable deterioration in the health of the participants in the study.

Particularly important was the increase in incidence of hepatitis B, which rose from 11.1% to 30%,

and the incidence of hepatitis C, which increased from 1.7% to 15.3%. In addition, from 1989 to 1993 opiate misusers had more venereal disease, epileptic seizures, and suicide attempts; used more additional drugs such as codeine, barbiturates, and benzodiazepines; and were more likely to be jobless and homeless. One of the few favourable results was that the proportion of misusers positive for HIV declined slightly, from 3.7% to 2.7%.

Professor Michael Krausz, the lead author of the study, called for more detoxification programmes and for them to offer methadone treatment, which remains a controversial approach in Germany. He also said that hepatitis vaccinations should become mandatory for drug misusers.

The police estimate that there are about 120 000 opiate and cocaine misusers in Germany and a similar number use so called designer drugs such as ecstasy. Between 1988 and 1996 the number of deaths related to drugs almost tripled from 670 to 1712 per year. □

Ban on pressurising Canadian doctors to work in remote areas

David Spurgeon, *Quebec*

The Canadian practice of pressurising doctors to work in remote areas has been ruled unconstitutional by the Supreme Court in the province of British Columbia.

Since 1995, doctors who have moved into areas that British Columbia's medical services commission deemed to have already too many doctors have received only 50% of the negotiated pay scale.

The two tiered billing system meant that fewer doctors moved into British Columbia—a province that is also experiencing soaring healthcare costs. Similar schemes have been adopted by other provinces.

The ruling means that British Columbia—and other provinces if their courts follow suit—will have to think of other ways of getting doctors to practise in remote areas, perhaps by

offering bonuses rather than penalties.

Madam Justice Risa Levine's ruling says the fee cutting mechanism violates doctors' rights to mobility and equality under Canada's charter of rights and freedoms.

She also said that the system violates the Canada Health Act, which underlies the national Medicare system, because the measures "do not provide reasonable compensation for all insured services." And in favouring British Columbia's residents over those from elsewhere, the mechanism is also clearly discriminatory, she added.

Since the plan was introduced, 204 of the 839 new doctors have received only half of their scheduled fees. The province has a total of 8000 doctors. □

Three days needed to recover from head injuries

Kamran Abbasi, *BMJ*

Athletes who have sustained mild head injuries should not be allowed to play again until at least three days after the symptoms have disappeared a recent study suggests.

The researchers, from the University of North Carolina, claim that although healing after a head injury takes more than a week, the first few days are crucial in allowing athletes' balance to recover and prevent further injury (*Medicine and Science in Sports and Exercise* 1997;29, (suppl 7):S213-21).

Just last month a former team doctor at Tottenham Hotspur football club claimed that he had lost his job because he tried to stop the German star Jürgen Klinsmann from playing with a head injury. Patrick Keating said that the club had ignored his demand for the player to see a brain specialist after he had been knocked unconscious during a match. Dr Keating lost his claim for unfair dismissal.

The researchers used a \$70 000 (£44 000) device that was first used to study how astronauts adapted to weightlessness in order to assess the balance of athletes with mild head injuries. These results were compared with those of a control group of uninjured volunteers. Even though tests of cognition were normal in the athletes in the head injury group, their balance remained significantly impaired for three days afterwards.

The athletes tested were American footballers, wrestlers, and lacrosse and soccer players. A mild head injury was deemed to have occurred if the athlete was conscious within 20 minutes, the period of amnesia lasted for less than 24 hours, and there was no radiographic abnormality. Any athletes staying in hospital for longer than 48 hours were excluded from the study.

Dr Kevin Guskiewicz, assistant professor of physical educa-



Even when cognition appears normal, balance may be impaired

tion and sports science at the University of North Carolina, said: "Our study is the first to look at balance in athletes with

acute mild head injuries and the first to show that balance can be impaired even when tests of cognition are normal." □

Is this the end of research as we know it?

Stephen Proctor has pioneered an innovative research method involving whole populations. He tells Adam Legge why this approach, rather than randomised controlled trials, is the way forward



Professor Proctor ruffles the feathers of the orthodoxy

If you want to set up a trial looking at a disease of comparatively low incidence then current thinking demands you do a multi-centre randomised controlled trial. You set up a protocol, send it round, and hope other clinicians will join up. With luck you might get up to a third of the patients in the country.

Of course there will be an element of selection, and patients in another centre are unlikely to be managed exactly in the same way as yours. There will be patients you can't include, such as those who are too old or have atypical disease. They will not be included and therefore their progress will not be tracked.

This, according to Stephen Proctor, is just not good enough. He is professor of haematological medicine at the Royal Victoria Infirmary in Newcastle and is arguably the leading voice challenging megatrials as the gold standard for studying disease, in

his case haematological malignancies. His alternative has been to develop a network of 28 haematology specialists in a distinct geographical area—the old Northern region. They have regular face to face meetings and aim to treat patients in a common coherent way.

Most importantly, they ensure that every new patient with a haematological malignancy is included in a disease register. This is nothing like the usual cancer register, which Professor

Proctor likens to “the capital letter at the start of a sentence and the full stop at the end.”

Rather, it includes detailed personal, prognostic, and diagnostic information, clinical management, and outcomes for every patient in the 3 million

population. The register is maintained and histopathology checked by a full time medically qualified member of the team. This ensures that any clinical study the group carries out deals with a completely representative population with large enough numbers to ensure power. Meanwhile each consultant uses what Professor Proctor calls the menu, a guide to treatment evolved by the group.

The strategy is called population adjusted clinical epidemiology (PACE), and it aims to improve the standard and consistency of treatment for all patients, not just those deemed suitable to enter a randomised trial.

“I was studying haematology here from 1974, and by 1980 I knew I was going to stay. My boss persuaded me that there was a potential academic gold mine here,” he says.

What working in Newcastle provided him with was a defined geographical base and a group of haematologists who were keen to cooperate, plus “no politics and lots of good fun.” So now haematologists from the Scottish borders down to Middlesbrough and across to west Cumberland meet regularly to review research, carry out audit, and socialise.

The key to the process has been the group's ability to dispense with politics. “The data are doctor collected and doctor owned. They are collected on patients all the doctors have an interest in and handled by people with whom they have an affinity and trust. Nobody's played off against each other,” says Professor Proctor.

The approach is an innovative one, but he has found allies in the old North West, Merseyside, and Oxford regions who now collaborate to produce research on a population of around 13 million people. Consultants in two other regions—South East Thames and West Midlands—have also started to collect data in the same way in the past two years.

“We are dealing with reality based medicine”

He is aware that he ruffles the feathers of the orthodoxy. “If Richard Smith [editor of the *BMJ*] sent a paper of ours to a Medical Research Council person to be reviewed it would be bounced,” he says. “We're seen as competitors, which we're not, and

also as attacking the randomised controlled trial, which we're not. But what we do causes trouble even if we try to explain it gently, which we do, because it's perceived as attacking the classical trial style.”

His criticisms of megatrials is that they are often performed on selected and biased populations, which are recruited non-randomly from a patient population of attenders at specialist centres. This led to a lack of good quality research in his area of interest throughout the 1980s.

“People say of Medical Research Council trials: ‘Oh, they must be getting the right answer because they've got the numbers.’ But they're not if they're selecting from 15% of the patient population,” he says.

“Randomised clinical trials work on simple interventions and homogeneous populations. They do work in childhood leukaemia but that's because you've got a homogeneous population, so small that there are a limited number of doctors, all of whom meet each other regularly.”

Professor Proctor is aware of the limitations of population adjusted clinical epidemiology and says that generally doctors working in London do not like it because they do not deal with patients in a geographically limited base. Whole population coverage is essential for this approach. It is also not easy to see how such an approach could work in a high incidence disease such as hypertension.

But the approach is being extended into other, more common diseases, such as breast cancer. This is starting in greater Tyneside, where specialists in breast cancer are starting to enter all patients in a register.

“We are starting in a smaller geographical area but we will then expand. Breast cancer specialists here are drooling at the thought of being part of the only place in the world that has total data,” he says.

All people have to do to grasp the beauty of this approach is to appreciate the advantage of looking at a whole population, he insists. “What we are dealing with is reality based medicine. Evidence based medicine is going to influence those it's going to influence but what about the others—elderly people and those with atypical disease? What we're trying to do is hold those patients in a reality based way.” □