Diabetes research for developing countries

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"It is essential that the public, both in the industrial and the developing countries, appreciate the full measure of the dangers of diabetes. It is the poor and the marginalized in our societies who are maimed and killed by this eminently treatable disease. It must take its rightful place at the top of our priorities."

Ismail Serageldin

Summary

EAGLES investigations into the specific needs for diabetes research in developing countries, and Europe's potential to support that research, reach nine major conclusions.

In each case, they involve tuning European research to have the greatest impact in the shortest possible time, by understanding and respecting developing countries' conditions of health, politics and economics. Major recommendations arise from the lack of *national population based epidemiology* to enable planning and convince political powers of the need for action; from countries' low health care budgets – entailing needs for the *cheapest possible interventions*; from the need to investigate interventions *specifically tuned to national circumstances*; and finally from the needs for specific *local biomedical research*, such as studies into the several unique African phenotypes of the disease.

The details of our nine recommendations can be seen at the end of the report.

Introduction

Eighty per cent of people with diabetes in the world live in developing countries, where the number of people with diabetes is predicted to increase by 150% in the next 25 years, according to the World Health Organization (WHO). Even in the next ten years, diabetes deaths will increase 50% without urgent action. And the International Diabetes Federation (IDF) estimates that 3.8 million people died as a result of diabetes in 2007. This is more than deaths from HIV/AIDS and nearly four times the deaths from malaria.

And yet the WHO – and to a greater extent the developing countries themselves – are struggling to deal with the problem, as with other chronic diseases in the developing world, with tiny resources and very little relevant research. WHO headquarters itself has but one expert devoted to diabetes – partly a reflection of the interests of the major donors.

What is diabetes?

Untreated – as is often the case in the poorest communities - diabetes can result in blindness, kidney failure, amputations of lower limbs, and death. Some 80% of the 3.8 million diabetes deaths annually are believed to be occurring in low- and middle-income countries, according to WHO experts.

Diabetes follows failure in the body's use of sugar, which is controlled by the hormone insulin, produced by the pancreas – a long gland near the stomach.

Type 1 diabetes most often arises in childhood, when an autoimmune attack on the pancreas halts insulin production; type 2 diabetes usually arises later in life, when the body becomes insensitive to the insulin that the pancreas produces.

Type 2 diabetes is much more common than type 1 diabetes, and accounts for around 90% of all diabetes worldwide.

A third type of diabetes is gestational diabetes, first recognized during pregnancy.

Type 1 diabetes is directly treatable only with injected insulin. Type 2 may be managed with a combination of diet, pharmaceuticals (by mouth or injection), and insulin supplementation

So in this context, what should Europe be doing for developing countries, in supporting research for diabetes?

What do developing countries want?

Perhaps the best way to find out what research developing countries need is to ask them. To discover their broad themes of interest, EAGLES talked to leading diabetes researchers and practitioners in countries in Asia and Africa.

Cameroon

Professor Jean Claude Mbanya, President-Elect of the International Diabetes Federation, spoke to EAGLES from the low-middle-income country Cameroon - one of the few well-studied developing countries thanks to a European Union research programme comparing diabetes in Africans in Cameroon, the Caribbean and the UK in 1994. "In 1998, [in a study supported by the UK's Department for International Development] the prevalence of diabetes was about 2%," said Mbanya. "In 2003 [in a study supported by the World Diabetes Foundation, WDF[1]] it was already 5%, and 2007 [in another WDF study] it is going to be about 6.5%".

It's a dramatic rate of increase, and it extends to the rural areas, "where you get so many people now with impaired glucose tolerance, and impaired fasting glycaemia" – precursors of diabetes.

"If you look at obesity, which is one of the major risk factors for diabetes in Cameroon – it's about 16% in the rural areas. And nearly 30% in the urban areas" said Mbanya. This appears to be the first result of a small degree of development.

"What you used to call rural is not like rural today, because of access to communications, roads, mobile telephone networks, television access and all the rest; so there is competition among the different foodstuffs even in the rural areas. And then the mentality in most of Africa is that what is Western is better."

"Nutrition is changing to include more refined carbohydrate, rather than the complex carbohydrates they used to eat – easy accessibility to rice, for example, are displacing the tubers that they used to eat. They will sell the tubers to buy the rice, for example!"

"But I don't think it's mostly nutrition, I think it's mostly a more sedentary lifestyle - a change of physical activity. It's the Chinese phenomenon of having motorbikes everywhere. Where they used to walk to places, now they have a bike."

So what's to be done? "I think first of all you need to produce data to convince the government. That's what's been done. I think it also helps very much when you have a local champion – because he or she at least can work towards the achievement of certain goals. And also you need a team, like mine, to carry out the surveys and assist the government."

Surveys then are key – proper, population-based epidemiological surveys – launched in Cameroon by an interest in Europe in studying diabetes in its immigrant populations, showing that high diabetes rates in these people were primarily environmental. But the interest waned, and studies have been continued by the World Diabetes Foundation, an independent foundation

[1] http://www.worlddiabetesfoundation.org

set up through a grant from Novo Nordisk, a Danish company which is one of the world's three major producers of insulin, the essential treatment for genetic childhood 'type 1' diabetes and for some cases of the primarily adult 'type 2' diabetes [see Box 'What is diabetes?'].

Economic studies are also crucial. "Some data, no matter how it is collected, is better than no data!" said Mbanya. "You can do hospital analysis of admissions, bed occupancy and deaths, for chronic diseases and the rest. Over a period of time you would see that the greatest burden is maybe diabetic foot – the foot ulcer; they stay in hospital for three months, or the foot is amputated. If you look at the economic burden imposed by diabetic foot on the hospital, you'll see that it chops off a whole chunk of the budget! It's more than malaria, tuberculosis, AIDS and the rest! It's a priority therefore to deal with that!"

Kenya

In Kenya, researcher and medical practitioner Kitirda Acharya told EAGLES: "We have started collecting data. We're probably ten years behind, but it's better late than never, and we're actually working closely with the Ministry of Health." (Such liaisons ensure that some political note is taken of the work, instead of a research paper languishing unnoticed in a journal.)

"A lot of the data is still in raw form and we need to process it, but basically we are coming out with prevalence rates of diabetes nationally and it's an alarming figure, it's higher than HIV/Aids. We're picking up prevalence rates of 11%." Also, said Acharya "We have done surveys in rural Kenya as well as urban Kenya, and we find that the prevalence rates are almost at par."

"Now Kenya is quite cosmopolitan, especially in the urban areas" she said, "and we have a big influx especially of Asian communities, of which I am one. And I find again in my private practice it's extremely, extremely prevalent. In every Asian family there are two or three people with type 2 diabetes over the age of 30 years."

Low birth weight babies are at higher chance of developing type 2 diabetes later on in life, and this may account for the high rates in rural areas in Kenya, Acharya believes. "The poorer communities are in the rural areas, so maybe we are condemning foetuses or babies before they're born to diabetes because of poor nutrition during the mother's pregnancy."

There may also be genetic effects showing differences among various tribes – a great melting pot of variation for research, which may shed light on diabetes worldwide – another potential target for EU support.

Sri Lanka

Dr. Mahen Wijesuriya, Chair of the IDF South East Asian Region, speaking from Rajagiriya, Sri Lanka, told EAGLES that two million people had diabetes in his country, out of a population of 20 million – a rate of 10%. In the urban population 16% - one person in six – has diabetes, and in the rural areas it is about 8%. "And the figures might double by the year 2025" said Wijesuriya.

There is a similar pattern in India and Bangladesh, he says – "All of us are running around 16-20% in the urban population – we are the double-digit boys."

Public health care in Sri Lanka is well known to be good, and that applies also to diabetes, but more primary

prevention is needed, and for the complications – the eye, the kidney and the foot – "we have care in quality but not in quantity" said Wijesuriya.

As for research, Wijesuriya emphasised the value of "translation research" – where investigation is made of how to translate academic research into practical action. So with IDF support Sri Lanka is investigating the development of proven life-style risk factors – such as poor nutrition and little exercise – in children, "where we have committed ourselves to intervene in life-style changes, over three years".

"We want to use these [risk] factors to see if we can bring down the incidence and prevalence of diabetes in our community" said Wijesuriya.

"We hope to make this a landmark study where others could follow" he said – opening up another opportunity for EU research, to support IDF or others in similar translational studies in a wide variety of cultures and countries. These studies to create positive interventions could be made on the basis of the "four agreed major [causes] of diabetes: genetic factors, intrauterine nutrition [principally poor nutrition of the pregnant mother], life-style after birth – and mental stress".

What about research to bring down the cost of treatments (primarily drugs for type 2 diabetes, and insulin injections for type 1), asked EAGLES?
"Now you've hit upon the sensitive point. Drugs we can manage, because there are generics. Although there are manufacturers in India and possibly China producing cheaper insulin, there are supply interruptions and we still are dominated by the Eli Lilly group and the Novo Nordisk group. They maintain the prices. When they got human [cloned] insulin, we all thought it was a bonanza and we were going to get enough cheap insulin. But the price never came down, and it is now going up, again away from the poor man's pocket. That is where something an be done from the richer part of the world, with equitable distribution of production, and cost-factor analysis."

"We don't want the insulin producing companies to go broke. But we want good insulin, cheap." The original, pre-cloning bovine[2] insulin had problems, causing reactions in some people, said Wijesuriya, not because of biochemical differences from human insulin, but because of impurities; porcine insulin was better but can't be used in Muslim communities. We feel we have to deal with human insulin only.

Regarding the price of medical human insulin, Anil Kapur, Managing Director of WDF, told EAGLES however that the market price was already low, and that to cover the poorest household countries must provide or organize some kind of social security.

"Manufacturers, particularly Novo Nordisk, offer insulin to 50 least developed countries at 20% the price in the West" said Kapur. "But governments are not able to buy adequate quantities to meet their demands at even these prices - or if they buy, there are local mark ups and taxes which hike up the price.

"Also, through leaks in the public system, the low priced product goes to the private market - where it is sold at high price," said Kapur. "The tender

[2] *Within vertebrates, the similarity of insulin is extremely close. Bovine insulin differs from human in only three amino acid residues, and porcine insulin in one. Even insulin from some species of fish is similar enough to human to be effective in humans.*

price of human insulin today is actually lower than price of animal insulin adjusted for inflation."

"The other issue is that there is no reimbursement, or effective health insurance, so at whatever low price it is available for people living on less than a dollar a day it is unaffordable. So the issue is not insulin pricing but creating effective health safety nets and covers" Kapur said."

So there's another target for the EU: insulin that the poorest can afford, by negotiation with the producers, or by research that creates cheaper production technologies, or by supporting effective health security for the poorest.

China

In China, Dr. Li Liu – a paediatric diabetes physician at Guangzhou Children's' Hospital - told EAGLES: "95% of the diabetes at this hospital is of course type 1. It's easy to diagnose here, but it's often misdiagnosed in the countryside, if they aren't aware of it, for things like nausea and abdominal pain." [This is a consequence of the ketoacidosis that follows a diabetic child's lack of natural insulin.]

In consequence, a lot of her patients arrive late – and unconscious, in a coma, says Li. The first need of all her patients is medical insulin, she says. But they must pay – and a lot of them have to have insurance cover. "It's very expensive compared to their income," she said. "So some of them give up the treatment." And the child dies.

It costs US$700 for the first visit, and then US$40-70 for a period of treatment – usually about a month - until they become stable, using insulin injections and blood sugar tests, said Li. "Then they go home, and then they have to continue the treatment, injecting at least twice a day for life, and testing their blood sugar" said Li, at a cost of around US$40-70 per month.

"We have many neonatal cases, and sometimes the parents give up" she said. "They think the children will face education problems, marriage problems, and employment problems… You know in China parents prefer sons. I met a nine-year old patient, a girl, and her parents were very poor and they said she would cost us a lot of money… we will raise another child, and not continue treatment. And some diabetics when they reach puberty want to commit suicide."

"Recently, there was news here in China of a diabetic student who passed her entrance to university – but when they discovered she was diabetic they asked her to go home." That is against government policy "but the universities, and employers, always find many, many reasons to refuse". The reason: universities and employers are obliged to pay their students' or employee's medical costs. It's the price of insulin again.

Research is needed on how best to educate the population about diabetes, said Li, to let them know that "diabetics are not a big problem for them –we can manage it very well".

Tanzania

In Tanzania, physician and researcher Dr. Kaushik Ramaiya stressed the need for population-based epidemiology of diabetes. "We have nothing significant outside South Africa, Tanzania and Cameroon" he told EAGLES. "We need help to get these basic epidemiological studies done, to identify the state of the problem… Then we need to get the risk factor profiles."

"We also need to strengthen the healthcare system itself – infrastructure, tools to make the diagnosis, like a basic ophthalmoscope for eye problems. You need tools to identify and diagnose the complications." But totally new tools aren't needed – just the availability of the one we've already got. "And then you need the training how to use them."

"Health systems research could identify the gaps within the resources, in the training, in the equipment, and find ways to fill up those gaps" he said. "We also need to improve the supply and logistics systems, especially for life-saving drugs like insulin. We need insulin at an affordable cost, but them we need to get it from urban right out to rural areas."

"We use ceramic pots, with water, underground in a very cool place, to store the insulin out there." [It must be kept below 30ºC to remain active; a similar, two-skin pot has been developed by diabetes NGO, the DREAM Trust, in India.]

India

Dr. Shaukat Sadikot, President, Diabetes India, told EAGLES: "Everyone will tell you the problem is prevention; it's important, but quite frankly the problem in India right now is that a lot of people who have diabetes don't even know they've got it. So they present with complications."

"For example we did an all-India study about eight years ago, published in 2004, going into the villages and tribal areas and everywhere, and we found that in the rural areas, which we defined as places with populations under 100 000, four out of five people with diabetes didn't know it. Even in the major cities, it was one out of two. So one of the main things is to inform people."

"The other problem that we face in developing countries is that 98-98% of patients are treated only by family physicians, and that doesn't mean someone who studied allopathic [modern] medicine. It might be someone who's done ayurvedic or homeopathic medicine and so on…. So the basic problem is creating awareness – amongst the doctors and amongst the public."

So there are very simple things that can be done, said Sadikot – like checking for maculopathy (macular decay, a diabetic complication which leads to blindness in the central part of the eye) with a simple eye test card. "And we have the Jaipur foot, for amputees. A good foot costs US$8 000. But a modified Jaipur foot costs US$25-30. Why can't India establish 20 centres to provide them across India?", Sadikot asked.

But these things are not being implemented "because chronic diseases have not come into the focus of the ministry… India spends 0.9% of its expenditure on health. Less even than Mali. For a country like ours it's absurd".

As for research, "We keep doing these studies, and after that no-one takes it on", Sadikot told EAGLES. "And imagine I'm the minister. Even if I want to take on diabetes management and prevention, the effects won't show for 10-15 years, and I know I'm not going to be in still the job. If I were the health minister – or the finance minister – I know I'm going to face an election in five years, so I'm going to do something that gives me mileage right now, like being seen giving polio drops to people and all those things."

But the Australian government had taken no notice of diabetes – until they made some economic studies that showed its effect on health costs and the economy, by taking working-age people out of work, EAGLES pointed out.

"Yes. But here… You do a study that shows that diabetes is the major cause of blindness. Or that it's the second largest cause, after accidents, of amputations of the lower leg. Or that out of every four patients undergoing kidney transplants, one is a diabetic. And 70-80% of the cost is born by the patients themselves. And 40% of our population earns less than US$1 a day."

As for insulin "I'm on the Insulin Task Force, and we still have insulin available, with one vial containing 400 units, and it's cheap because two or three Indian companies began making it and the prices definitely fell. It's not cheap enough for a very poor person, but in the type of society that we have, Diabetes India is able to give free insulin to poor children."

"I'd tell the EU that India has the largest number of people with diabetes; that we have cheap and cost-effective solutions that could be useful even in Europe; but that the only problem here is that *awareness* amongst the patients and family physicians is lacking, on proper management, and that is what needs to be looked into right now."

So you need to identify effective communication campaigns? "Absolutely. And for the doctors. I'm a physician. We don't want complex information – we want to know simple things. A patient walks into my clinic with high blood sugar. What do I do? How do I adjust doses? What do I look out for? We have enough studies now! When are we going to get out of that academic loop and do something with the people on the ground?"

Some practical recommendations from the South

Diabetes physicians and NGOs in developing countries come up with many, simple proposals for practical products that if they were available to them, would make a great difference. All that's needed is to ask. Here are just two that were proposed to EAGLES:

- Develop, produce, and make available low cost strips for blood glucose testing. "Boehringer Manheim had a strip which changed color, which we used to use only with color matching to get an approximate test in our poorer patients. It meant we could cut strips into 2-3 longitudinal segments, and did not need a meter, and therefore did not need to worry about meter batteries running out, or meter malfunction. Unfortunately they phased it out three years ago."

- Develop, produce, and make available low cost safety devices for the 'sharps' used in blood tests and insulin injection. "For example, a 'Safeclip' costs US$ 5, which is ridiculous, and they won't even market it for those who can afford it in India. Cheaper alternatives could easily be developed and their impact studied in rock bottom poor communities."

The position in Europe

European diabetes epidemiology

Carinne de Beaufort, a Dutch paediatric endocrinologist and diabetologist in Luxembourg, told EAGLES "I may sound rude, but there's such a lack of comparable data on diabetes within

Europe we should clean our own house first! Take blindness, one of the main complications of diabetes. If you look at how many countries have a good population-based information set on that – on blindness among people with diabetes - it might be just *one* country! We don't have comparable data – we are comparing a lot of eggs with apples."

"We made a review in 2000-2, and I was shocked!" said de Beaufort. "Lots of countries don't collect national health statistics at all. Some are based on hospital admissions, some on discharge; some ignore diabetes; some include it because they earn a special grant for diabetic patients. You can now see clearly what is known and not know, on a website, for the European Core Indicators on Diabetes,[3] based on 19 countries."

"What I think the EU must impose some rules – say 'we must collect', not that 'we want to collect' good statistics. A Council of Ministers decision. Everyone thinks the statistics are reliable, and they haven't got a clue what they are looking at!"

"The data is vital, because when you take an action for health you want to know whether a change has happened! How can you if you haven't got a clue what you are looking for! You have to start with reliable data and then the rest will follow. We in Europe need to set an example."

[3] http://www.eucid.eu

The view from industry

Lars Rebien Sørensen, the *CEO of the leading insulin producer - the Danish company Novo Nordisk - is candid about his company's interest. He told EAGLES at a World Diabetes Foundation meeting in Nairobi "I don't like philanthropy – it's the rich saving their consciences." But by supporting projects in developing countries, "I said to my shareholders: we will inspire our staff; we will get more staff; we will gain respect with patients' groups; and these countries are growing."*

Good, realistic arguments for a profit-making company; but wouldn't it be better if - in addition- there were support from public sources, like the European Union, for some major epidemiology in key countries in the developing world, to clarify problems and help convince national and donor governments that action was needed -without any lingering doubts about motives, however unjustified they might be.

European research

The objective of the €6.1 billion (US$9.4 billion) health research component of the Seventh Framework Programme, the current 2007-2013 European Union research programme, is 'to improve the health of European citizens and boost the competitiveness of health-related industries and businesses, as well as address global health issues'.[4]

[4] http://cordis.europa.eu/fp7/health/home_en.html

In the preceding Framework Programme 6 (FP6) for research, close to €200 million Euros [US$ 300 million at current exchange rates] were devoted to diabetes/obesity research, and 'Diabetes and obesity are again part of our health research funding in FP7', Manuel Hallen, Acting Director for Health Research at the Commission, told EAGLES. But precise amounts devoted to diabetes in FP7 can't be determined immediately, because it will depend on the quality of proposals, the competition for funding among applicants, and the roll-out during FP7 of specific 'calls for tender' for research, which barring the first, which has already been made, are still being negotiated.

However, says the Commission's Health Directorate, 'the diabetes research currently being funded by the Commission does not explicitly address diabetes in the developing countries'.

Also, explains the Directorate, 'the limited overall funding for the programme requires us to make sometimes difficult prioritisations, and with regard to the developing world and its health problems, the focus has been on infectious diseases and public health research.'

But here there's the question – which comes first, the chicken or the egg? The Commission Health Directorate tells EAGLES that 'because of the nature and the dimensions of diabetes in developing countries, in terms of political challenges, it is important to reach a situation where developing countries acknowledge the problem and include it on their list of health priorities'. But it is clear from our investigations in these countries that their governments will certainly not recognize the problem until it has been measured by clear, population based epidemiology in their own country – research in which the EU could well assist.

Even with such studies, of course, governments may still not recognize the problem - as we heard from Dr. Shaukat Sadikot of Diabetes India – but without them there is almost no likelihood of them taking the disease seriously. So here it's a case of science first – policies later.

Meanwhile 'In general, work on diabetes [in FP7] focuses on aetiologies [causes] of the different types of diabetes, and their related prevention and treatment' the Health Directorate told EAGLES. 'For obesity, the focus will be on multidisciplinary approaches including genetics, life style and epidemiology.' And for both diabetes and obesity, 'special attention will be given to juvenile diseases and factors operating in childhood'.

Nevertheless, 'the proposers are free to include partners from [developing countries] in their projects'. So for future support from Europe a lot may depend on developing country diabetes and obesity researchers finding, making or employing existing relationships with European partners, particularly – given the questions raised in our inquiries - on epidemiology.

Also, the Health Directorate encouragingly tells EAGLES, 'In future calls in FP7 there might be specific topics addressing the issue in countries in development, both low and middle-income countries'. So there is room also to influence the Commission towards developing country needs in future programmes. 'It is clear to us that the epidemic of type 2 diabetes is affecting the whole world, rich and poor countries alike' the Directorate told EAGLES. 'In the world ranking of diabetes burden

[among adults], several developing countries [have an incidence] of 10% and higher. These include, for example, Egypt and Mexico.'
There is also a route to research support as an 'International Cooperation Partner Country'.[5]

'In the current Framework Programme the rules for international participation in our programme, meaning the participation of non-associated, non EU countries, has been greatly increased, in particular for the so-called International Cooperation Partner Countries, which include all low and medium income countries.'

'It is our hope that with time there will be more international partners in the projects so that a scientific problem can be addressed from different angle on a global level. Acknowledging that the cures and therapies are normally universal and applicable for all humans, we hope to contribute to the solution or at least reduction of the disease burden.'

'On top of this we might consider opening specific topics, not least in the public health sector, to address issues such as access to therapies or socio-economic factors.'

Here again the Commission is demonstrating its openness to ideas for relevant research from developing countries – a welcome sign. But it will be necessary for those with relevant ideas to contact the Commission to present them.[6]

Also some specific calls for research in diabetes and obesity have already been made. In general, these 'first calls' (with deadlines for application of 19 April 2008) are for biomedical investigations, but they include invitations to researchers to create 'a road map for diabetes research'. This calls for the preparation of a 'broad review of the entire state-of-the art science in the EU with respect to all types of diabetes. Identification of existing programmes in Member States, recent research advances, and identification of gaps'.

Perhaps in such a survey there will be an opportunity for the winners to think a little more broadly, and consider the potential impact of Europe's research on the global epidemic of diabetes and obesity?

It would be up to those who would like to influence the survey in that direction to contact the winner – the EURADIA (Alliance for European Diabetes Research) project 'DIAMAP' to discuss the issues at stake.[7]

'There have already been meetings with – for example - China and Russia to discuss possible future topics related to diabetes, with emphasis on those countries' the Health Directorate explains. Furthermore 'with regard to the least developed countries, such as some countries in Africa, the issue might also be addressed in the context of public health and access to medicines, as sometimes the main problem in those countries is not *de novo* research but simply the lack of application of already established medical practice and affordable drugs.'

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5 http://ec.europa.eu/research/iscp/pdf/icpc_countries_en.pdf

6 *The best points of contact are national members of the 'Programme Committee' for Health – contact the Commission for more details.*

7 See http://www.euradia.org or contact Professor Philippe Halban (Coordinator), Chairman of EURADIA, Rheindorfer Weg 3, 40591 Düsseldorf, Germany.

The €10m [US$ 15m] project InterAct[8], investigating how biologically plausible genetic and lifestyle behavioural factors, particularly dietary intake and physical activity, interact to lead to the development of type 2 diabetes - and so what preventive action could be taken - is such an example. Funded under the research Framework Programme 6, it already includes an Indian partner, Prof. A Ramachandran, Director of the Indian Diabetes Research Foundation, Chennai. "We've been the only people to do a prospective, randomized control trial on the primary prevention of type 2 diabetes in India" Professor Ramachandran told EAGLES.

Even average-weight South-East Asians are prone to diabetes, unlike Caucasians, and the study – the Indian Diabetes Prevention Programme - focused on them.

Published in 2006[9], it showed that quite *moderate* and practical lifestyle modifications – such as some exercise, and a reduction of fat and increase in fruit and fibre in the diet – can reduce type 2 diabetes by 30% in non-obese Indian people, even without significant weight loss.

In that and a following study Ramachandran also took and stored around 900 blood samples for later genetic analysis and follow-up for the incidence of diabetes.

Under the InterAct project he will analyse correlations between these and response to the lifestyle changes, in collaboration with an institute in Hyderabad.

He says however that the support from Europe "just enough" for sample storage handling, together with secretarial and statistical assistance. "We could do with funds to do the complete genetic analysis in India" Ramachandran told EAGLES. "And we'd like to do further analysis on some biomarkers, for which we need infrastructure and equipment." Europe usually only pays for staff and other expenses, he says "but with infrastructure it would be real development as we'd continue our research with that even if they stop funding later".

Ramachandran also believes Europe potentially has a great deal to learn from supporting genetic and lifestyle epidemiological research in India, as significant genetic components to type 2 diabetes should be identifiable in the Indian population, which could have significance to all peoples. "If we are going to strike a gene for type 2 diabetes, we may be able to strike that here first, rather than in the Caucasian population where the prevalence rate is much less" he said.

[8] InterAct website: http://www.inter-act.eu - and see box.

[9] A. Ramachandran *et al., Diabetologia.* 2006 Feb;49(2):289-97.

The European project InterAct investigates…

…the interaction between genes and environment in the development of type 2 diabetes. Claudia Langenberg, of the project HQ in Cambridge, told EAGLES: "We're looking at all new cases of diabetes in the [Europe-wide] EPIC study. We've got about 17 000, way more than we expected." For all these there are blood samples. Other recent studies have identified "so far!" about 16 genes associated with type 2 diabetes, and InterAct will correlate these with behavioral traits.

But this is "potentially the largest case-control study of diabetes in the world", says Langenberg, so InterAct may also do a genome-wide scan of up to a million random genetic markers – to see if they can pick up new associations.

"If we find a gene that only increases risk, say, in people who are obese, we can ask a powerful question of real trials – did people respond differently, according to their genotype?" This is the kind of work that will be done with India, and various European countries said Langenberg. "For the future we are also looking at China" she said.

Africa is also very interesting, she said, as it shows different 'sub-phenotypes' of diabetes – different presentations of the disease. But so far it lacks the intervention studies that InterAct could work with.

Conclusions

Inquiries with leading international diabetes researchers and medical practitioners, and in particular in some representative developing countries, have demonstrated that the prime research, development – and supply - needs are these:

- Reliable population-based epidemiological studies of diabetes, to measure the true scale of the problem, its existing and potential economic impact (on hospitals and nationally).

- Research to improve the functioning of health systems in developing countries, to deliver effective prevention measures, and diagnosis and care for diabetics. Even the simplest treatment, with little reason to be costly, is often unavailable or unaffordable due to local constraints.

- Research to develop means for the self-management of chronic diseases, including diabetes – a field in which Europe has previously shown interest. This could be of value to low-resource settings, if account were taken of the relevant social and economic settings.

- Practical R&D and design work for simple products like test strips and safety devices that would be affordable in developing countries.

- Especially for paediatric type 1 diabetes, research to discover means for providing affordable and reliable supplies of insulin and medication to the poorest of patients.

- 'Translational research', that takes diabetes' principal causative factors as known, and tests practical interventions against those factors that - if proven - might be adopted.

- Intervention studies, investigating different means of reducing diabetes incidence and caring for cases - in particular in Africa, where such studies are lacking.

- Studies of the unique diabetes phenotypes in Africa.

- Infrastructure and equipment support for research on genetic markers for type 2 diabetes in the non-obese South Asian population.

For all of these, but especially the first – the epidemiological and economic impact surveys – it will be extremely important to design the studies *in cooperation with the local government*, so the study 'belongs' to them from the outset. Such studies are always received more seriously than ones without government cooperation that simply 'appear' in the literature. Within Europe, EAGLES has learned that comparable studies in countries – essential to check the impact of interventions - are also lacking.

In the current Framework Programme 7 research strategy of the European Union; although current diabetes research covers none of the above, we have learned several entry points for future work for developing countries, which those countries – and those in Europe who are interested in those countries – should pursue:

- Not least, within FP7 the EU is open to *broad recommendations* from developing countries for research relevant to their diabetes and obesity problems, *especially to shape future 'calls for tender'* in these fields. The EU recognizes the scale of the problem in developing countries. However, it is implied that such recommendations would be taken more seriously if the *developing country governments* themselves asked for support for such research (the EU being an organization of governments). However, the governments are unlikely to take diabetes and obesity seriously until population-based epidemiological and economic studies are made *with their cooperation*; so there is a delicate, 'chicken and egg' diplomatic question to bridge. No studies, no requests; but no requests, no studies. Potential research partners in developing countries might begin by forging good connections with their own governments, and then making joint approaches to FP7 for support.

- In the existing and future calls for tender for research proposals, European researchers are free to include developing country partners; and in particular one research proposal currently under call, to map the future of diabetes research, could be critical to ensure future EU research in these fields is global in scope.

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Picture: World Health Organisation (WHO)

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