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Compiled By Ralph Turchiano
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Conflicts of Interest

WHO and the pandemic flu "conspiracies"

Deborah Cohen, features editor, BMJ, Philip Carter, journalist, The Bureau of Investigative Journalism, London

dcohen@bmj.com

Key scientists advising the World Health Organization on planning for an influenza pandemic had done

paid work for pharmaceutical firms that stood to gain from the guidance they were preparing. **These conflicts of interest have never been publicly disclosed by WHO, and WHO has dismissed inquiries into its handling of the A/H1N1 pandemic as "conspiracy theories."** Deborah Cohen and Philip Carter investigate

Next week marks the first anniversary of the official declaration of the influenza A/H1N1 pandemic. On 11 June 2009 Dr Margaret Chan, the director general of the World Health Organization, announced to the world's media: "I have conferred with leading influenza experts, virologists, and public health officials. In line with procedures set out in the International Health Regulations, I have sought guidance and advice from an Emergency Committee established for this purpose. On the basis of available evidence, and these expert assessments of the evidence, the scientific criteria for an influenza pandemic have been met...The world is now at the start of the 2009 influenza pandemic."

It was the culmination of 10 years of pandemic preparedness planning for WHO—years of committee meetings with experts flown in from around the world and reams of draft documents offering guidance to governments. **But one year on, governments that took advice from WHO are unwinding their vaccine contracts, and billions of dollars' worth of stockpiled oseltamivir (Tamiflu) and zanamivir (Relenza)—bought from health budgets already under tight constraints—lie unused in warehouses around the world.**

A joint investigation by the BMJ and the Bureau of Investigative Journalism has uncovered evidence that raises troubling questions about how WHO managed conflicts of interest among the scientists who advised its pandemic planning, and about the transparency of the science underlying its advice to governments. Was it appropriate for WHO to take advice from experts who had declarable financial and research ties with pharmaceutical companies producing antivirals and influenza vaccines? Why was key WHO guidance authored by an influenza expert who had received payment for other work from Roche, manufacturers of oseltamivir, and GlaxoSmithKline, manufacturers of zanamivir? **And why does the composition of the emergency committee from which Chan sought guidance remain a secret known only to those within WHO?** We are left wondering whether major public health organisations are able to effectively manage the conflicts of interest that are inherent in medical science.

Already WHO's handling of the pandemic has led to an unprecedented number of reviews and inquiries by organisations including the Council of Europe, European Parliament, and WHO itself, following allegations of industry influence. Dr Chan has dismissed these as "conspiracies," and earlier this year, during a speech at the Centers for Disease Control and Prevention in Atlanta, she said: "WHO anticipated close scrutiny of its decisions, but we did not anticipate that we would be accused, by some European politicians, of having declared a fake pandemic on the advice of experts with ties to the pharmaceutical industry and something personal to gain from increased industry profits."

The inquiry by British MP Paul Flynn for the Council of Europe Parliamentary Assembly—due to be published today—will be critical. It will say that decision making around the A/H1N1 crisis has been lacking in transparency. **"Some of the outcomes of the pandemic, as illustrated in this report, have been dramatic: distortion of priorities of public health services all over Europe, waste of huge sums of public money, provocation of unjustified fear amongst Europeans, creation of health risks through vaccines and medications which might not have been sufficiently tested before being authorised in fast-track procedures, are all examples of these outcomes. These results need to be critically examined by public health authorities at all levels with a view to rebuilding public confidence in their decisions."**

The investigation by the BMJ/The Bureau reveals a system struggling to manage the inherent conflict between the pharmaceutical industry, WHO, and the global public health system, which all draw on the same pool of scientific experts. **Our investigation has identified key scientists involved in WHO pandemic planning who had declarable interests, some of whom are or have been funded by pharmaceutical firms that stood to gain from the guidance they were drafting. Yet these interests have never been publicly disclosed by WHO and, despite repeated requests from the BMJ/The Bureau, WHO**

has failed to provide any details about whether such conflicts were declared by the relevant experts and what, if anything, was done about them.

It is this lack of transparency over conflicts of interests—coupled with a documented changing of the definition of a pandemic and unanswered questions over the evidence base for therapeutic interventions¹—that has led to the emergence of these conspiracies.

WHO says: "Potential conflicts of interest are inherent in any relationship between a normative and health development agency, like WHO, and a profit-driven industry. Similar considerations apply when experts advising the Organization have professional links with pharmaceutical companies. Numerous safeguards are in place to manage possible conflicts of interest or their perception."

Another factor that has fuelled the conspiracy theories is the manner in which risk has been communicated. No one disputes the difficulty of communicating an uncertain situation or the concept of risk in a pandemic situation. But one world expert in risk communication, Gerd Gigerenzer, director of the Centre for Adaptive Behaviour and Cognition at the Max Planck Institute in Germany, told the BMJ/The Bureau: "The problem is not so much that communicating uncertainty is difficult, but that uncertainty was not communicated. **There was no scientific basis for the WHO's estimate of 2 billion for likely H1N1 cases, and we knew little about the benefits and harms of the vaccination. The WHO maintained this 2 billion estimate even after the winter season in Australia and New Zealand showed that only about one to two out of 1000 people were infected. Last but not least, it changed the very definition of a pandemic.**"

WHO for years had defined pandemics as outbreaks causing "enormous numbers of deaths and illness" but in early May 2009 it removed this phrase—describing a measure of severity—from the definition.²

The beginnings

The routes to the Council of Europe's criticisms can be traced back to 1999, a pivotal year in the influenza world. In April that year WHO—spurred on by the 1997 chicken flu outbreak in Hong Kong—began to organise itself for a feared pandemic. It drew up a key document, Influenza Pandemic Plan: The Role of WHO and Guidelines for National and Regional Planning.

WHO's first influenza pandemic preparedness plan was stark in the scale of the risk the world faced in 1999: "It is impossible to anticipate when a pandemic might occur. Should a true influenza pandemic virus again appear that behaved as in 1918, even taking into account the advances in medicine since then, unparalleled tolls of illness and death would be expected."

In the small print of that document it states: "R Snacken, J Wood, L R Haaheim, A P Kendal, G J Ligthart, and D Lavanchy prepared this document for the World Health Organization (WHO), in collaboration with the European Scientific Working Group on Influenza (ESWI)." What this document does not disclose is that ESWI is funded entirely by Roche and other influenza drug manufacturers. Nor does it disclose that René Snacken and Daniel Lavanchy were participating in Roche sponsored events the previous year, according to marketing material seen by the BMJ/The Bureau.

Dr Snacken was working for the Belgian ministry of public health when he wrote about studies involving neuraminidase inhibitors for a Roche promotional booklet. And Dr Lavanchy, meanwhile, was a WHO employee when he appeared at a Roche sponsored symposium in 1998. His role at that time was in the WHO Division of Viral Diseases. Dr Lavanchy has declined to comment.

In 1999 other members of the European Scientific Working Group on Influenza included Professor Karl Nicholson of Leicester University, UK, and Professor Abe Osterhaus of Erasmus University in the Netherlands. These two scientists are also identified in Roche marketing material seen by this investigation which was produced between 1998 and 2000. Professor Osterhaus told the BMJ that he had always been

transparent about any work he has done with industry. Professor Nicholson similarly has consistently declared his connections with pharmaceutical companies, for example, in papers published in journals such as the *BMJ* and *Lancet*.

Both experts were also at that time engaged in a randomised controlled trial on oseltamivir supported by Roche. The trial was subsequently published in the *Lancet* in 2000.³ It remains one of the main studies supporting oseltamivir's effectiveness—and one that was subsequently shown to have employed undeclared industry funded ghostwriters.¹

The influence of the European Scientific Working Group on Influenza would continue as the decade wore on and the calls for pandemic planning became more strident. Founded in 1992, this "multidisciplinary group of key opinion leaders in influenza aims to combat the impact of epidemic and pandemic influenza" and claims links to WHO, the Robert Koch Institute, and the European Centre for Disease Prevention and Control, among others.⁴ Despite the group's claims of scientific independence its 100% industry funding does present a potential conflict of interest. One of its roles is to lobby politicians, as highlighted in a 2009 policy document.⁵

At a pre-pandemic preparation workshop of the European Scientific Working Group on Influenza in January last year, Professor Osterhaus said: "I can tell you that ESWI is working on that idea [that is, convincing politicians] quite intensively. We have contact with MEPs [members of the European Parliament] and with national politicians. But it is they who have to decide at the end of the day, and they will only act at the request of their constituencies. If the latter are not prompted, nothing will happen."

The group's policy plan for 2006-10 specifically stated that government representatives needed to "take measures to encourage the pharmaceutical industry to plan its vaccine/antivirals production capacity in advance" and also to "encourage and support research and development of pandemic vaccine" and to "develop a policy for antiviral stockpiling." It also added that government representatives needed to know that "influenza vaccination and use of antivirals is beneficial and safe." It said that the group provided "evidence based, palatable information"; and also "networking/exchange with other stakeholders (eg, with industry in order to establish pandemic vaccine and antivirals contracts)." In the meantime, in Roche's own marketing plan, one goal was to "align Roche with credible third party advocates". They "leveraged these relationships by enlisting our third-party partners to serve as spokespeople and increase awareness of Tamiflu and its benefits."⁶

Barbara Mintzes, assistant professor in the Department of Pharmacology and Therapeutics at the University of British Columbia, is currently part of a group working with Health Action International and WHO developing model curricula for medical and pharmaceutical students on drug promotion and interactions with the industry, including conflicts of interest. She thinks that caution is advised when working with medical bodies of this sort.

"It is legitimate for WHO to work with industry at times. But I would have concerns about involvement with a group that looks like it is for independent academics that is actually mainly industry funded," she told the *BMJ/The Bureau*, adding: "The Institute of Medicine has raised concerns about the need to have a firewall with medical groups. To me this does not sound like an independent group, as it is mainly funded by manufacturers."

She also thinks that there is a difference between the conflict of interest in having a clinical trial funded by a company and the conflict of interest in being involved in marketing a drug—for example, on a paid speaker's bureau or in marketing material. "Some academic medical departments, for example Stanford University, have banned staff from being involved in marketing or being on a paid speakers bureau," she said.

The presence of leading influenza scientists at promotional events for oseltamivir reflected not just the concern of an impending pandemic, but the excitement over the potential of a new class of drugs—neuraminidase inhibitors—to offer treatment and protection against seasonal influenza.

In 1999 two new drugs first came to market: oseltamivir, from Roche; and zanamivir, manufactured by what is now GlaxoSmithKline. The two drugs would battle it out over the coming years, with oseltamivir—aided by its oral administration—trumping its rival in global sales as the decade wore on.

The potential was quickly grasped. Indeed, that year Professor Osterhaus published an article proposing the use of neuraminidase inhibitors in pandemics: "Finally, during a possible future influenza pandemic, in view of their broad reactivity against influenza virus neuraminidase subtypes and the expected lack of sufficient quantities of vaccine, the new antivirals will undoubtedly have an essential role to play in reducing the number of victims."⁷

However, he also warned that antivirals should not be seen as a replacement for vaccinations. "Close collaboration and consultation between, on the one hand, companies marketing influenza vaccines and, on the other, those marketing antivirals will therefore be absolutely essential. It is important that a clear and uniform message indicating the complementary roles of vaccines and antivirals is delivered."

That article appeared in the European Scientific Working Group on Influenza's bulletin of April 1999; Professor Osterhaus signs off with the affiliation of WHO National Influenza Centre Rotterdam, The Netherlands.

Other experts soon followed suit—recommending the role neuraminidase inhibitors could play in any future pandemic—in both the academic literature and in the general media.

Food and Drug Administration

While the excitement over these drugs fuelled scientific symposiums, the US Food and Drug Administration (FDA) was less than convinced. The BMJ/The Bureau has since spoken to people from within the American and European drug regulators, the FDA and the European Medicines Agency (EMA), who said that both regulators struggled with the paucity of the data presented to them for zanamivir and oseltamivir, respectively, during the licensing process. At the end of last year, the BMJ called for access to raw data for key public health drugs after the Cochrane Collaboration found the effectiveness of the drugs impossible to evaluate.⁸ The group are continuing to negotiate access to what they say they need to fully assess the effectiveness of antivirals.

In the US, the FDA first approved zanamivir in 1999.⁹ Michael Elashoff, a former employee of the FDA, was the statistician working on the zanamivir account. He told the BMJ how the FDA advisory committee initially rejected zanamivir because the drug lacked efficacy.

After Dr Elashoff's review (he had access to individual patient data and summary study reports) the FDA's advisory committee voted by 13 to 4 not to approve zanamivir on the grounds that it was no more effective than placebo when the patients were on other drugs such as paracetamol. He said that it didn't reduce symptoms even by a day.

"When I was reviewing the data, I tried to replicate the analyses in their summary study reports. The issue was not of data quality, but sensitivity analyses showed even less efficacy," he said. "The safety analysis showed there were safety concerns, **but the focus was on if Glaxo had demonstrated efficacy.**" **Dr Elashoff's view was that zanamivir was no better than placebo—and it had side effects.** And when the FDA medical reviewer made a presentation, her conclusion was that it could either be approved or not approved. It was a fairly borderline drug.

There were influenza experts on the FDA's advisory committee and much of the discussion hinged on why a drug that looked so promising in earlier studies wasn't working in the largest trials in the US. One hypothesis was that people in the US were taking other drugs for symptomatic relief that masked any effect of zanamivir. So zanamivir might have no impact on symptoms over and above the baseline medications that people take when they have influenza.

Two other trials—one in Europe and one in Australia— showed a bit more promise. But there was a very low rate of people taking other medications. "So in the context of not being allowed to take anything for symptomatic relief, there might be some effect of Relenza. But in the context of a typical flu, where you have to take other things to manage your symptoms, you wouldn't notice any effect of Relenza over and above those other things," Dr Elashoff said. The advisory committee recommended that the drug should not be approved.

Nevertheless, FDA management decided to overturn the committee's recommendation.

"They would feel better if there was something on the market in case of a pandemic. It wasn't a scientific decision," Dr Elashoff said.

While Dr Elashoff was working on the zanamivir review, he was assigned the oseltamivir application. But when the review **and the advisory committee decided not to recommend zanamivir, the FDA's management reassigned the oseltamivir review to someone else. Dr Elashoff believes that the approval of zanamivir paved the way for oseltamivir, which was approved by the FDA later that year.**

European Medicines Agency

In Europe the EMEA was similarly troubled by the evidence for oseltamivir. By early 2002 Roche had sought a European Union-wide licence from the EMEA. It was a lengthy process, taking three meetings of the Committee for Medicinal Products for Human Use as well as expert panels, according to one of the two rapporteurs, Pekka Kurki of the Finnish Medicines Agency. Echoing the Cochrane Collaborations's 2009 findings⁶ Kurki told us: "We discussed the same issues that are still discussed today: does it show clinically significant benefits in treatment and prophylaxis of flu and what was the magnitude of the benefits presented in the RCTs? Our assessment and Cochrane's in 2009 are very similar with regard to the effect size in RCTs. **The data show that the effects of Tamiflu were clear but not very impressive.**

"What was unclear and is still unclear is what is the impact of Tamiflu on serious complications. Circulating influenza was very mild when Tamiflu was developed and therefore it is very difficult to say anything about serious complications. The data did not clearly show an effect on serious complications—it was not demonstrated by the RCTs."

In documents obtained under the freedom of information legislation, two of the experts who provided opinions during the EMEA licensing process have also featured in Roche marketing material: Annike Linde and Rene Snacken. In Dr Snacken's EMEA presentation dated 18 February 2002, he discussed the need for chemoprophylaxis and called for the use of oseltamivir during a pandemic. He made his presentation as a representative of the Belgian Ministry of Public Health. At the time Dr Snacken was also "liaison officer" for the European Scientific Working Group on Influenza. He also played a key role in the Belgian government during its pandemic planning, and he later became a senior expert at the Preparedness and Response Unit, European Centre for Disease Prevention and Control. We do not know what, if anything, he declared to the EMEA about his relationship with Roche.

Anniko Linde has confirmed in an email that she has had connections with Roche over a number of years. She made a presentation to the EMEA on "influenza surveillance" in her capacity as a representative of the Swedish Institute for Infectious Disease. Again, it is not clear what, if anything, she declared to the EMEA concerning her previous relationship with Roche.

Dr Linde, now the Swedish state epidemiologist, has told the BMJ/The Bureau that she received payments from Roche International in respect of various pieces of work she did for the company until 2002. She has subsequently given occasional lectures for Roche Sweden. All money she has received from Roche was given, Dr Linde says, to the Swedish Institute for Infectious Disease Control.

We asked the scientists whether they declared their relationship with Roche at the time to the EMEA.

Neither has answered that question entirely satisfactorily. Dr Snacken has not replied to repeated emails posing this question. Dr Linde responded by telling the BMJ/The Bureau: "We contribute with our expertise to the regulatory agencies when asked. When we do so, a declaration of interest, where e.g. participation at advisory meetings at Roche, is given and evaluated by the regulatory agency." The BMJ/The Bureau requested Linde and Snacken's declaration of interest statements for the 2002 meeting from the EMEA under the freedom of information act. The EMEA was unable to provide statements for those particular people at that time.

Developing the guidelines

In October 2002 WHO convened a meeting of influenza experts at its Geneva headquarters. Their purpose was to develop WHO's guidelines for the use of vaccines and antivirals during an influenza pandemic.

Included at this meeting were representatives from Roche and Aventis Pasteur and three experts who had lent their name to oseltamivir's marketing material (Professors Karl Nicholson, Ab Osterhaus, and Fred Hayden).

Two years later the WHO published a key report from that meeting, WHO Guidelines on the Use of Vaccines and Antivirals during Influenza Pandemics 2004. The specific guidance on antivirals, Considerations for the Use of Antivirals During an Influenza Pandemic, was written by Fred Hayden. Professor Hayden has confirmed to the BMJ/The Bureau in an email that he was being paid by Roche for lectures and consultancy work for the company at the time the guidance was produced and published. He also told us in an email that he had received payments from GlaxoSmithKline for consultancy and lecturing until 2002. According to Prof Hayden: "DOI [declaration of interest] forms were filled out for the 2002 consultation."

The WHO guidance concluded that: "Based on their pandemic response goals and resources, countries should consider developing plans for ensuring the availability of antivirals. Countries that are considering the use of antivirals as part of their pandemic response will need to stockpile in advance, given that current supplies are very limited." Many countries around the world would adopt this guidance.

The previous year Professor Hayden was also one of the main authors of **a Roche sponsored study that claimed what was to become one of oseltamivir's main selling points—a claimed 60% reduction in hospitalisations from flu, which the Cochrane Collaboration was later unable to verify.**⁸

Our investigation has also identified relevant and declarable interests relating to the two other named authors of annexes to WHO's 2004 guidelines. Arnold Monto was the author of the annexe dealing with vaccine usage in pandemics. Between 2000 and 2004—and at the time of writing the annexe—Dr Monto has consistently and openly declared honorariums, consultancy fees, and research support from Roche, 10 11 12 consultancy fees and research support from GlaxoSmithKline 10 12 13 14; and also research funding from ViroPharma.¹⁵

No conflict of interest statement was included in the annex he wrote for WHO. When asked if he had signed a declaration of interest form for WHO, Dr Monto told the BMJ/The Bureau: "Conflict of Interest forms are requested before participation in any WHO meeting".

Professor Karl Nicholson is the author of the third annex, Pandemic Influenza. According to declarations made by Professor Nicholson in the BMJ¹⁶ and Lancet in 2003,¹⁷ he had received travel sponsorship and honorariums from GlaxoSmithKline and Roche for consultancy work and speaking at international respiratory and infectious diseases symposiums. Before writing the annexe, he had also been paid and declared ad hoc consultancy fees by Wyeth, Chiron, and Berna Biotech.

Even though the previous year these declarations had been openly made in the Lancet and the BMJ, no conflict of interest statement was included in the annex he wrote for WHO. Professor Nicholson told the BMJ/The Bureau that he last had "financial relations" with Roche in 2001. When asked if he had signed a

declaration of interest form for WHO, Prof Nicholson replied: "The WHO does require attendees of meetings, such as those held in 2002 and 2004, to complete declarations of interest."

Leaving aside the question of what declarations experts made to WHO, one simple fact remains: WHO itself did not publicly disclose any of these conflicts of interest when it published the 2004 guidance. It is not known whether information about these conflicts of interest was relayed privately to governments around the world when they were considering the advice contained in the guidelines.

The year before WHO issued the 2004 guidance, it published a set of rules on how WHO guidelines should be developed and how any conflicts of interest should be handled. This guidance included recommendations that people who had a conflict of interest should not take part in the discussion or the piece of work affected by that interest or, in certain circumstances, that the person with the conflict should not participate in the relevant discussion or work at all. The WHO rules make provision for the director general's office to allow declarations of interest to be seen if the objectivity of a meeting has been called into question.¹⁸

The BMJ/The Bureau has asked WHO for the conflict of interest declarations for the Geneva 2002 meeting and those related to the guidance document itself. WHO told us that the query went directly up to **Margaret Chan's office. "WHO never publishes individual DOIs [declaration of interest], except after consultation with the Office of the Director-General. In this case, we put in a request on your behalf but it was not granted. In more recent years, many WHO committees have published summaries of relevant interests with their meeting reports."**

In a BMJ interview (see film on bmj.com), WHO spokesperson Gregory Hartl reiterated the fact that Dr Margaret Chan, "is very committed personally to transparency." Yet her office has turned down repeated requests for declaration of interest statements and declines to comment on the allegations that authors of the guidelines had declarable interests.

Nevertheless, Prof Hayden told the BMJ/The Bureau: "I strongly support transparency in declarations of interest, in part because this allows those reading documents, particularly ones authored by specific individuals (eg, Annex 5) [the part he wrote], to make their own judgments about the possible relevance of any potential conflicts."

While experts need to work with industry to develop the best possible drugs for illnesses, questions remain about what level of involvement experts with industry ties should have in the formulation of public health policy decisions and guidelines. Professor Nicholson told the BMJ/The Bureau: "The WHO and decision makers must be informed of ongoing developments and research findings to ensure that they are as up to date as possible. Some of the most relevant expertise and information are held by companies or individuals with conflicts of interest. I understand the view that experts with conflicts of interest should not advise governments or organisations such as the WHO. But to exclude such people from discussions could deprive WHO and decision makers of important new information."

But not everyone agrees. Barbara Mintzes is unequivocal about what role they should play. "No one should be on a committee developing guidelines if they have links to companies that either produce a product—vaccine or drug—or a medical device or test for a disease. It would be preferable that there are no financial ties when it comes to making big decisions on public health—for example, stockpiling a drug—and that includes if they have a currently funded clinical trial," she said.

"Ideally, what you want are independent experts who are in the public sector to provide expertise on drugs and vaccines. But they can be hard to find. One solution is consult with the experts who are involved in industry, but not put them on any decision making committee. You need a firewall," she added.

Indeed, Professor Harvey Fineberg, president of the Institute of Medicine and chairman of the panel reviewing WHO's management of the pandemic, takes a similarly hard line. His own institution went through a detailed review of how they interact with industry and experts with conflicts of interests last year.¹⁹ "Sometimes publication of conflict of interests is enough—for example with a journal. But if you

are giving expert judgment to influence policy, revealing is not enough," he told the BMJ, referring to the Institute of Medicine's policy.

WHO also says that it takes conflicts of interests seriously and has the mechanisms in place to deal with them. But what action does it take when a scientist declares a conflict of interest, and when does it judge a scientist to be too conflicted to play a leading role in the formulation of global health policy? Since WHO has not provided us with an answer to this question, we are left to guess.

As it stands, this situation is the worst possible outcome for WHO, according to Professor Chris Del Mar, a Cochrane Review author and expert on WHO's Strategic Advisory Group of Experts on Immunization group. "If it proves to be the case that authors of WHO guidance which promoted the use of certain drugs were being paid at the same time by the makers of those drugs for other work they were doing for these companies that is reprehensible and should be condemned in the strongest possible terms."

WHO's endorsement of oseltamivir was not lost on Roche. In an advert placed by the company for the drug in the main conference programme of the European Scientific Working Group on Influenza's 2005 conference in Malta, it says: "Antivirals will initially be the principal medical intervention in a pandemic situation and Roche is working as a responsible partner with governments to assist in their pandemic planning." The source reference for this is the WHO Global Influenza Preparedness Plan.

Throughout the following years, WHO would appear to have been inconsistent in how it treated conflicts of interest. Updated pandemic plans would continue to be prepared by experts who openly had work funded and acted as consultants to manufacturers of vaccines and antivirals. WHO produced its global influenza preparedness plan in 2005, and in 2006 it constituted an interim Influenza Pandemic Task Force. No public declarations of interest have been made and to date no details have been provided by WHO in response to our requests.

WHO's stance that it does not publish declarations of interest from its experts is far from consistent. It is undermined, for example, by the position WHO adopts in relation to the Strategic Advisory Group of Experts on Immunization, its standing vaccine advisory body. Here, contrary to its approach to pandemic planning advisers, WHO does publish summaries of declarations of interest.

Emergency Committee

These seeming inconsistencies in WHO's approach to transparency and its handling of conflicts of interest extend into the workings of the Emergency Committee formed last year to advise the director general on the pandemic. The identities of its 16 members are unknown outside WHO. This secret committee has guided WHO pandemic policy since then—including deciding when to judge that the pandemic is over.

WHO says it has to keep the identities secret to protect the scientists from being influenced or targeted by industry. In a phone call to the BMJ/The Bureau in March, WHO spokesperson Gregory Hartl explained: "Our general principle is we want to protect the committee from outside influences."

The committee advised the WHO director general on phase changes as well as temporary recommendations. According to WHO, When the Emergency Committee met to discuss a possible move to a declaration of a pandemic, the meeting additionally included members who represented Australia, Canada, Chile, Japan, Mexico, Spain, the UK, and the US, eight countries that experienced widespread outbreaks at the time. These national representatives were present to ensure full consideration of the views and possible reservations of the countries expected to bear the initial brunt of economic and social repercussions.

WHO says all members of the Emergency Committee sign a confidentiality agreement, provide a declaration of interests, and agree to give their consultative time freely, without compensation. However, only one member of the committee has been publicly named: Professor John MacKenzie, who chairs it.

This is a troubling stance: it suggests that WHO considers other advisory groups whose members are not anonymous—such as the Strategic Advisory Group of Experts on Immunization—to be potentially subject to outside influences, and it allows no scrutiny of the scientists selected to advise WHO and global governments on a major public health emergency.

Under the International Health Regulations framework, the membership of the Emergency Committee is drawn from a roster of about 160 experts covering a range of public health areas. This framework provides guidelines about how WHO deals with acute public health risks. The BMJ/The Bureau has identified approximately 15 scientists from the International Health Regulations roster with influenza expertise and has emailed them to ask if they were on the Emergency Committee. Under the framework at least some of these scientists are members of the Emergency Committee. Yet because of the confidentiality agreements they have signed, these scientists cannot acknowledge their membership of the committee, putting them in an invidious position.

David Salisbury, chair of WHO's Strategic Advisory Group of Experts on Immunization (SAGE) committee at the time of the pandemic and a member of the International Health Regulations, says the secrecy has caused problems for his group. "It certainly caused problems for SAGE. Since all of the details of SAGE are in the public domain, there was a perception that it had been SAGE that had given advice about the changing of definitions or the pandemic levels—when we had not done so. SAGE members came in for unfair personal abuse by journalists," he told the BMJ/The Bureau.

"Given the importance of the advice, the transparency of the source of the advice was important. I believe it is necessary to keep confidential the source of advice if revealing details might put individuals at risk, for example when bioterrorism is being discussed. This does not seem to be the case for pandemic flu," he added.

The secrecy of the committee is also fuelling conspiracy theories, particularly around the activation of dormant pandemic vaccine contracts. A key question will be whether the pharmaceutical companies, which had invested around \$4bn (£2.8bn, 3.3bn) in developing the swine flu vaccine, had supporters inside the emergency committee, who then put pressure on WHO to declare a pandemic. It was the declaring of the pandemic that triggered the contracts.

The BMJ/The Bureau can confirm that Dr Monto, Dr John Wood, and Dr Masato Tashiro are members of the Emergency Committee.

Although Dr Monto did not answer the question directly, his Infectious Disease Society of America biography states that he is a member.²⁰

Last year, according to figures made public in the US by GlaxoSmithKline, Professor Monto received \$3000 speakers fees from the company in the period between the second quarter and the last quarter of 2009. As a national official of the Japanese government, Dr Tashiro says that he must "have nothing concerning conflict of interest with private companies". Dr John Wood works for the UK National Institute for Biological Standards and Control (NIBSC). Dr Wood, like Dr Tashiro, has no personal conflict of interests but he told the BMJ/The Bureau that as part of its statutory role in developing standards for measurement of biological medicines to ensure accurate dosing and carrying out independent control testing to assure their safety and efficacy, the institute must work closely with the pharmaceutical industry. This is made clear on their website.

"The International Federation of Pharmaceutical Manufacturers and Associations has also made publicly available the nature of their close interaction with NIBSC and similar organisations in order to develop influenza vaccines," he said.²¹

Those who said that they were not on the committee include David Salisbury, Alan Hampson, Albert Osterhaus, Donato Greco, and Howard Njoo. Maria Zambon, from the UK's Health Protection Agency told the BMJ: "I undertake various advisory roles to WHO. Declaration of interest statements are prepared before undertaking such roles.

"The HPA Centre for Infection, as part of its role in national infectious disease surveillance, provision of specialist and reference microbiology and vaccine efficacy monitoring, works closely with vaccine manufacturers and biotechnology companies."

International Health Regulations review

WHO's own review into the operation of the International Health Regulations and WHO's handling of the pandemic is now being conducted by Harvey Feinberg, president of the US Institute of Medicine, and will report its findings next year. Dr Chan and Professor Feinberg have both made clear the need for a thorough investigation. But questions are already arising about how independent the review will turn out to be. According to the International Health Regulations list in our possession, some 13 of the 29 members of the review panel are members of the International Health Regulations itself and one is the chair of the Emergency Committee. To critics that might suggest a somewhat incestuous approach.

Professor Mintzes does not agree with WHO's explanation that secrecy was needed to protect against the influence of outside interest on decision making. "I can't understand why the WHO kept this secret. It should be public in terms of accountability like the expert advisory committees. If the rationale of secret membership is not to be unduly influenced, there are other ways of dealing with this through strong conflict of interest provisions," she said.

She also believes that the very nature of allowing a trigger point for vaccine contracts opens the system up unnecessarily to exploitation. "It seems a problem that this declaration might trigger contracts to be realised. There should be safeguards in place to make sure those with an interest in vaccine manufacturers can't exploit the situation. The WHO will have to look long and hard at this in future," she said.

The number of victims of H1N1 fell far short of even the more conservative predictions by the WHO. It could, of course, have been far worse.. Planning for the worst while hoping for the best remains a sensible approach. But our investigation has revealed damaging issues. If these are not addressed, H1N1 may yet claim its biggest victim—the credibility of the WHO and the trust in the global public health system.

Cite this as: BMJ 2010;340:c2912

Competing interests: PC declares no competing interests. DC has been paid expenses by WHO for giving talks at two conferences.

Public release date: 31-May-2010

Antidepressants in pregnancy increase risk of miscarriage

A new study in CMAJ (Canadian Medical Association Journal) found a 68% increase in the overall risk of miscarriage in pregnant women using antidepressants (pre-embargo link only)
<http://www.cmaj.ca/embargo/cmaj091208.pdf> .

Antidepressants are widely used in pregnancy and up to 3.7% of women will use them at some point during the first trimester. Discontinuing treatment can result in a depressive relapse which can put mother and baby at risk.

Most previous studies on the use of antidepressants in pregnancy did not look at miscarriages as a main

outcome, had small samples and several showed contradictory results. This large study sought to determine the association between antidepressant use in pregnancy, including classes, types and doses, and the risk of miscarriage.

Researchers from the University of Montreal and the CHU Ste-Justine looked at data on 5124 women in Quebec from a large population-based cohort of pregnant women who had clinically verified miscarriages up to 20 weeks of gestation and a large sample of women from the same Registry who did not have a miscarriage. Of those who miscarried, 284 (5.5%) had taken antidepressants during pregnancy.

Selective serotonin reuptake inhibitors (SSRIs), especially paroxetine and also venlafaxine were associated with increased risk of miscarriage as were higher daily doses of either antidepressant. As well, a combination of different antidepressants doubled the risk of miscarriages.

"These results, which suggest an overall class effect of selective serotonin reuptake inhibitors, are highly robust given the large number of users studied," writes senior author Dr. Anick Bérard, from the University of Montreal and the Director of the Research Unit on Medications and Pregnancy at CHU Ste-Justine.

The researchers urge that physicians who have patients of child-bearing age taking antidepressants or have pregnant patients who require antidepressant therapy early in pregnancy discuss the risks and benefits with them.

Public release date: 31-May-2010

New Cancer Guidelines: Exercise During and After Treatment is Now Encouraged, Says Penn Medicine-Led Panel

“Avoid Inactivity” to Boost Quality of Life, Strength and Fitness

CHICAGO – Cancer patients who’ve been told to rest and avoid exercise can – and should – find ways to be physically active both during and after treatment, according to new national guidelines. Kathryn Schmitz, PhD, MPH, an associate professor of Epidemiology and Biostatistics and a member of the Abramson Cancer Center at the University of Pennsylvania School of Medicine, will present these guidelines at an educational session at the 2010 meeting of the American Society of Clinical Oncology, aimed at making cancer exercise rehabilitation programs as common as those offered to people who have had heart attacks or undergone cardiac surgery. (Exercise Testing and Prescription for Cancer Survivors: Guidelines from the American College of Sports Medicine)

Schmitz, whose previous research reversed decades of cautionary exercise advice given to breast cancer patients with the painful arm-swelling condition lymphedema, led a 13-member American College of Sports Medicine expert panel that developed the new recommendations after reviewing and evaluating literature on the safety and efficacy of exercise training during and after cancer therapy.

“We have to get doctors past the ideas that exercise is harmful to their cancer patients. There is a still a prevailing attitude out there that patients shouldn’t push themselves during treatment, but our message – avoid inactivity – is essential,” Schmitz says. “We now have a compelling body of high quality evidence that exercise during and after treatment is safe and beneficial for these patients, even those undergoing complex procedures such as stem cell transplants. If physicians want to avoid doing harm, they need to incorporate these guidelines into their clinical practice in a systematic way.”

Cancer patients and survivors should strive to get the same 150 minutes per week of moderate-intensity aerobic exercise that is recommended for the general public, the panel says. Though the evidence indicates

that most types of physical activity – from swimming to yoga to strength training – are beneficial for cancer patients, clinicians should tailor exercise recommendations to individual patients, taking into account their general fitness level, specific diagnosis and factors about their disease that might influence exercise safety. Cancer patients with weakened ability to fight infection, for instance, may be advised to avoid exercise in public gyms.

One persistent area of concern for cancer patients is change in body mass – both weight gain and weight loss tied to disease symptoms and treatment side effects. Patients with hormone-based tumors, breast and prostate cancers, tend to gain weight during treatment and frequently have difficulty losing it. Other patients, especially those with gastrointestinal tumors, suffer from weight loss brought on by loss of appetite and changes in their ability to swallow and properly digest food. The new guidelines indicate that both groups can benefit from exercise. Studies show, for instance, that exercise for weight control and reduction in body mass may actually reduce the risk of recurrence for breast cancer patients, and ultimately decrease breast cancer mortality. For patients suffering from cancer-related weight loss, physical activity helps to maintain lean body mass, which can contribute to increased strength and well being.

Schmitz and her colleagues analyzed published studies related to five different adult cancer types (breast, during and after treatment, prostate, hematologic – with and without stem cell transplant – colon, and gynecologic), and reviewed the evidence for multiple health outcomes. The panel found that although there are specific risks associated with cancer treatment that need to be considered when patients exercise, there is consistent evidence that exercise training can lead to improvements in aerobic fitness, muscular strength, quality of life and fatigue in breast, prostate, and hematologic cancer patients and survivors. They found the data for colon and gynecologic cancers were too scant to draw firm conclusions, and identified several areas requiring further study. Age, for instance, is a critical variable, Schmitz says, since more must be learned about the effects of physical activity in cancer patients over age 65, to develop interventions that may help these patients continue to live and function independently.

The panel urges fitness professionals to enhance their capacity to serve the unique needs of cancer survivors. Schmitz noted that a “groundswell” of training programs now assist physical therapists and fitness trainers in deepening their knowledge of the effects of cancer diagnosis and treatment and improve their skills in this emerging area.

Schmitz also feels strongly that practicing oncologists need to be informed about the new guidelines and their importance, and says that patients can play a role in changing attitudes and clinical practice. Her hope is that patients will read the recommendations and discuss them with their doctors, creating the demand for change that will drive more cancer centers and oncology practices to create and offer cancer exercise rehabilitation services.

Schmitz will present the new guidelines at an educational session on Sunday, June 6, from 4:45 to 6:00 p.m.

Patients are available, upon request, to discuss their experiences exercising during and after cancer treatment.

Public release date: 1-Jun-2010

Aspirin recommendations changed for many younger diabetic patients

CORVALLIS, Ore. – Experts are now recommending that low-dose aspirin therapy to prevent heart attacks be used somewhat more conservatively – **that men younger than 50 and women younger than 60, who have diabetes but no other major risk factors, probably not use aspirin.**

The new recommendations are based on an analysis of nine studies, which found that the risks of some side effects such as stomach bleeding, and to a much less extent bleeding strokes, have to be better balanced against the potential benefits of using aspirin.

The findings are agreed upon by a panel of experts and endorsed by the American Diabetes Association, the American Heart Association and the American College of Cardiology Foundation. They were just published online as a position statement in the journal Diabetes Care.

"The larger theme here is that use of low-dose aspirin to prevent heart attacks in people who have not already experienced one is probably not as efficacious as we used to believe it was," said Craig Williams, an associate professor in the College of Pharmacy at Oregon State University, and one of the experts on the recent review panel.

"With any medication, you have to balance the benefits against possible side effects or risks," Williams said. "But even a baby aspirin has some degree of risk, even though it's very low, so we have to be able to show clear benefits that outweigh that risk. In the case of young adults with diabetes but no other significant risk factors, it's not clear that the benefits are adequate to merit use of aspirin."

Aspirin first came to attention for its clear value in acute situations, or people experiencing a heart attack and immediately taking an aspirin. Later it was believed that regular low-doses of aspirin, which act as an anti-coagulant or blood thinner, may have value for people who have risk factors for heart disease, such as high blood pressure, smoking, a family history of cardiovascular disease, or other relevant health issues.

Diabetics also face higher risk of heart disease as they age, and it had been recommended by many doctors that diabetics use low-dose aspirin therapy along with their other medications. The newest recommendations suggest that aspirin be used only by diabetics who have other risk factors and are older – men older than 50 and women older than 60. A recent update to the U.S. Preventive Services Task Force is still recommending aspirin use for older adults who are not diabetics – ages 45-79 for men, 55-79 for women – and who have other risk factors.

"The newest studies just weren't showing adequate benefits for some younger diabetics," Williams said.

At least part of the issue, Williams said, is that widespread use of drugs to control blood pressure and reduce cholesterol has lessened the additional benefits of aspirin. For people who have high blood pressure or elevated cholesterol and are not taking appropriate medications to address those problems, aspirin use might be more justified, Williams said. However, generic statin medications for cholesterol and various hypertension treatments are now available at minimal costs, he said, and have to be considered as part of the optimal approach.

Williams said there is no evidence that higher doses of aspirin beyond the range of 75-162 milligrams per day have any added value in preventing heart attacks. An adequate level of protection is generally achieved with what's considered a "baby aspirin," usually sold in the U.S. as a pill of 81 milligrams, or one-fourth the strength of a typical 325 milligram single aspirin pill.

Additional studies in patients with diabetes are being conducted to further demonstrate exactly who would best benefit from aspirin therapy, Williams said.

Public release date: 2-Jun-2010

Peaches, plums induce deliciously promising death of breast cancer cells

COLLEGE STATION -- Breast cancer cells - even the most aggressive type - died after treatments with peach and plum extracts in lab tests at Texas AgriLife Research recently, and scientists say the results are deliciously promising. Not only did the cancerous cells keel over, but the normal cells were not

harmful in the process.

AgriLife Research scientists say two phenolic compounds are responsible for the cancer cell deaths in the study, which was published in the Journal of Agriculture and Food Chemistry. The phenols are organic compounds that occur in fruits. They are slightly acidic and may be associated with traits such as aroma, taste or color.

"It was a differential effect which is what you're looking for because in current cancer treatment with chemotherapy, the substance kills all cells, so it is really tough on the body," said Dr. David Byrne, AgriLife Research plant breeder who studies stone fruit. "Here, there is a five-fold difference in the toxic intensity. You can put it at a level where it will kill the cancer cells - the very aggressive ones - and not the normal ones."

Byrne and Dr. Luis Cisneros-Zevallos originally studied the antioxidants and phytonutrients in plums and found them to match or exceed the blueberry which had been considered superior to other fruits in those categories.

"The following step was to choose some of these high antioxidant commercial varieties and study their anticancer properties," Cisneros-Zevallos said. "And we chose breast cancer as the target because it's one of the cancers with highest incidence among women. So it is of big concern."

According to the National Cancer Institute, there were 192,370 new cases of breast cancer in females and 1,910 cases in males in 2009. That year, 40,170 women and 440 men died from breast cancer. The World Health Organization reports that breast cancer accounts for 16 percent of the cancer deaths of women globally.

Cisneros-Zevallos, an AgriLife Research food scientist, said the team compared normal cells to two types of breast cancer, including the most aggressive type. The cells were treated with an extract from two commercial varieties, the "Rich Lady" peach and the "Black Splendor" plum.

"These extracts killed the cancer cells but not the normal cells," Cisneros-Zevallos said.

A closer look at the extracts determined that two specific phenolic acid components - chlorogenic and neochlorogenic - were responsible for killing the cancer cells while not affecting the normal cells, Cisneros-Zevallos said.

The two compounds are very common in fruits, the researchers said, but the stone fruits such as plums and peaches have especially high levels.

"So this is very, very attractive from the point of view of being an alternative to typical chemotherapy which kills normal cells along with cancerous ones," Byrne added.

The team said laboratory tests also confirmed that the compounds prevented cancer from growing in animals given the compounds.

Byrne plans to examine more fully the lines of the varieties that were tested to see how these compounds might be incorporated into his research of breeding plums and peaches. Cisneros-Zevallos will continue testing these extracts and compounds in different types of cancer and conduct further studies of the molecular mechanisms involved.

Public release date: 2-Jun-2010

New evidence that chili pepper ingredient fights fat

Scientists are reporting new evidence that capsaicin, the stuff that gives chili peppers their kick, may cause weight loss and fight fat buildup by triggering certain beneficial protein changes in the body. Their study, which could lead to new treatments for obesity, appears in ACS' monthly Journal of Proteome Research.

Jong Won Yun and colleagues point out that obesity is a major public health threat worldwide, linked to diabetes, high blood pressure, heart disease, and other health problems. **Laboratory studies have hinted that capsaicin may help fight obesity by decreasing calorie intake, shrinking fat tissue, and lowering fat levels in the blood. Nobody, however, knows exactly how capsaicin might trigger such beneficial effects.**

In an effort to find out, the scientists fed high-fat diets with or without capsaicin to lab rats used to study obesity. **The capsaicin-treated rats lost 8 percent of their body weight and showed changes in levels of at least 20 key proteins found in fat. The altered proteins work to break down fats. "These changes provide valuable new molecular insights into the mechanism of the antiobesity effects of capsaicin," the scientists say.**

Public release date: 2-Jun-2010

Probiotic found in breast milk helps alleviate symptoms of digestive disorders

New research published in the FASEB Journal suggests **that Lactobacillus reuteri** immediately affects nerves in the gut, explaining how probiotics work

Here's another reason to breast feed your baby: Canadian researchers have discovered how a probiotic found in breastmilk **reduces or eliminates painful cramping in the gut**. In a new research report published online in the FASEB Journal (<http://www.fasebj.org>), these scientists use mice to show that a specific strain of **Lactobacillus reuteri decreases the force of muscle contractions in the gut within minutes of exposure**. This bacterium naturally occurs in the gut of many mammals and can be found in human breast milk. This discovery suggests that increasing the intake of this bacterium may help alleviate symptoms of a wide range of gut disorders, such as irritable bowel syndrome, inflammatory bowel disease, functional bowel disorders, and constipation.

"Scientifically and evidence-based approaches to nutrition to correct potential bacterial imbalance in the intestine and thereby promote better health and possibly restore health in diseases associated with these imbalances," said Wolfgang Kunze, a researcher involved in the work from the McMaster Brain-Body Institute and Department of Psychiatry at St. Joseph's Healthcare in Ontario, Canada.

To make this discovery, Kunze and colleagues, introduced Lactobacillus reuteri into isolated pieces of small intestine taken from healthy and previously untreated mice. The bacterium was added to a warm salt solution flowing through the lumen, or hollow part, of the intestine and the pressure caused by natural contractions was measured before, during and after adding the bacterium. Relaxation of smooth muscle tissue was compared with the action of the bacterium. Researchers also tested the electrical activity of single intestinal sensory nerve cells.

"It might not be possible for most of us to get breast milk from the tap," said Gerald Weissmann, M.D., Editor-in-Chief of the FASEB Journal, "but we can still benefit from some of the life-supporting substances it carries. This research shows that the relationship between humans and microbes can be beneficial for both. The Lactobacillus finds a new home, and we're no longer up tight."

Public release date: 3-Jun-2010

Autism finding could lead to simple urine test for the condition

Children with autism have a different chemical fingerprint in their urine than non-autistic children, according to new research published tomorrow in the print edition of the Journal of Proteome Research.

The researchers behind the study, from Imperial College London and the University of South Australia, suggest that their findings could ultimately lead to a simple urine test to determine whether or not a young child has autism.

Autism affects an estimated one in every 100 people in the UK. People with autism have a range of different symptoms, but they commonly experience problems with communication and social skills, such as understanding other people's emotions and making conversation and eye contact.

People with autism are also known to suffer from gastrointestinal disorders and they have a different makeup of bacteria in their guts from non-autistic people.

Today's research shows that it is possible to distinguish between autistic and non-autistic children by looking at the by-products of gut bacteria and the body's metabolic processes in the children's urine. The exact biological significance of gastrointestinal disorders in the development of autism is unknown.

The distinctive urinary metabolic fingerprint for autism identified in today's study could form the basis of a non-invasive test that might help diagnose autism earlier. This would enable autistic children to receive assistance, such as advanced behavioural therapy, earlier in their development than is currently possible.

At present, children are assessed for autism through a lengthy process involving a range of tests that explore the child's social interaction, communication and imaginative skills.

Early intervention can greatly improve the progress of children with autism but it is currently difficult to establish a firm diagnosis when children are under 18 months of age, although it is likely that changes may occur much earlier than this.

The researchers suggest that their new understanding of the makeup of bacteria in autistic children's guts could also help scientists to develop treatments to tackle autistic people's gastrointestinal problems.

Professor Jeremy Nicholson, the corresponding author of the study, who is the Head of the Department of Surgery and Cancer at Imperial College London, said: "Autism is a condition that affects a person's social skills, so at first it might seem strange that there's a relationship between autism and what's happening in someone's gut. However, your metabolism and the makeup of your gut bacteria reflect all sorts of things, including your lifestyle and your genes. Autism affects many different parts of a person's system and our study shows that you can see how it disrupts their system by looking at their metabolism and their gut bacteria.

"We hope our findings might be the first step towards creating a simple urine test to diagnose autism at a really young age, although this is a long way off - such a test could take many years to develop and we're just beginning to explore the possibilities. We know that giving therapy to children with autism when they are very young can make a huge difference to their progress. A urine test might enable professionals to quickly identify children with autism and help them early on," he added.

The researchers are now keen to investigate whether metabolic differences in people with autism are related to the causes of the condition or are a consequence of its progression.

The researchers reached their conclusions by using H NMR Spectroscopy to analyse the urine of three groups of children aged between 3 and 9: 39 children who had previously been diagnosed with autism, 28 non-autistic siblings of children with autism, and 34 children who did not have autism who did not have an autistic sibling.

They found that each of the three groups had a distinct chemical fingerprint. Non-autistic children with

autistic siblings had a different chemical fingerprint than those without any autistic siblings, and autistic children had a different chemical fingerprint than the other two groups.

Ralph's Note - Somebody better make up their mind. Currently they are crucifying scientist for even making the suggestion of the Gut Bacteria and Autism Connection.

Public release date: 3-Jun-2010

Key nutrient in maternal diet promises 'dramatic' improvements for people with Down syndrome

ITHACA, N.Y. – A nutrient found in egg yolks, liver and cauliflower taken by mothers during pregnancy and nursing may offer lifelong "dramatic" health benefits to people with Down syndrome .

A new study done at Cornell University and published June 2 in the peer-reviewed journal **Behavioral Neuroscience** found that **more choline during pregnancy and nursing could provide lasting cognitive and emotional benefits to people with Down syndrome. The work indicated greater maternal levels of the essential nutrient also could protect against neurodegenerative conditions such as Alzheimer's disease.**

"We found that supplementing the maternal diet with additional choline resulted in dramatic improvements in attention and some normalization of emotion regulation in a mouse model of Down syndrome," said lead author Barbara Strupp, professor of nutritional sciences and of psychology.

In addition to mental retardation, Down syndrome individuals often experience dementia in middle age as a result of brain neuron atrophy similar to that suffered by people with Alzheimer's disease. Strupp said the improved mental abilities found in the Down syndrome mice following maternal choline supplements could indicate protection from such neurodegeneration "in the population at large."

Strupp and her co-authors tested Down syndrome-model mice born from mothers that were fed a normal diet versus those given choline supplements during their three-week pregnancy and three-week lactation period. They also examined normal mice born from mothers with and without additional choline. The choline-supplemented mothers received about 4.5 times more choline (roughly comparable to levels at the higher range of human intake) than unsupplemented mothers.

Beginning at 6 months of age, the mice performed a series of behavioral tasks over a period of about six months to assess their impulsivity, attention span, emotional control and other mental abilities. The researchers found the unsupplemented Down syndrome-model mice became more agitated after a mistake than normal mice, jumping repeatedly and taking longer to initiate the next trial. The choline-supplemented Down syndrome-model mice showed partial improvement in these areas.

"I'm impressed by the magnitude of the cognitive benefits seen in the Down syndrome-model mice," Strupp said. "Moreover, these are clearly lasting cognitive improvements, seen many months after the period of choline supplementation."

Strupp said the results are consistent with studies by other researchers that found increased maternal choline intake improves offspring cognitive abilities in rats. However, this is the first study to evaluate the effects of maternal choline supplementation in a rodent model of Down syndrome.

Previous studies of humans and laboratory animals have shown that supplementing the diets of adults with choline has proven to be largely ineffective in improving cognition.

"Although the precise mechanism is unknown, these lasting beneficial effects of choline observed in the present study are likely to be limited to increased intake during very early development," Strupp said.

Public release date: 4-Jun-2010

Green tea extract appears to keep cancer in check in majority of CLL patients

Mayo Clinic has conducted the first clinical studies of tea extract in cancer patients
CHICAGO -- ASCO Abstract Number: 6522 (http://abstract.asco.org/AbstView_74_47574.html). An extract of green tea appears to have clinical activity with low toxicity in chronic lymphocytic leukemia (CLL) patients who used it in a phase II clinical trial, say researchers at Mayo Clinic.

The findings, to be presented Monday, June 7, during the annual meeting of the American Society of Clinical Oncology (<http://www.asco.org/>) (ASCO), are the latest in a series of Mayo studies to show promise for use of the chemical epigallocatechin gallate (EGCG) -- the major component of green tea -- in reducing the number of leukemia cells in patients with CLL. Mayo first tested EGCG in a variety of laboratory assays about eight years ago, and it was found to reduce the survival of CLL leukemic cells. This laboratory finding was followed by a successful phase I clinical trial -- the first time green tea extract had been studied in CLL patients.

"Although only a comparative phase III trial can determine whether EGCG can delay progression of CLL, the benefits we have seen in most CLL patients who use the chemical suggest that it has modest clinical activity and may be useful for stabilizing this form of leukemia, potentially slowing it down," says Tait Shanafelt, M.D. (<http://www.mayoclinic.org/bio/12787116.html>), a Mayo Clinic hematologist (<http://www.mayoclinic.org/hematology-rst/>) and lead author of the study.

"These studies advance the notion that a nutraceutical like EGCG can and should be studied as cancer preventives," says Neil Kay, M.D. (<http://www.mayoclinic.org/bio/13445391.html>), a hematology researcher whose laboratory first tested the green tea extract in leukemic blood cells from CLL patients. "Using nontoxic chemicals to push back cancer growth to delay the need for toxic therapies is a worthy goal in oncology research -- particularly for forms of cancer initially managed by observation such as CLL."

Drs. Shanafelt and Kay caution that EGCG is not a substitute for chemotherapy. All of the patients Mayo tested with EGCG were early stage, asymptomatic CLL patients who would not otherwise be treated until their disease progressed. The extract was supplied by the National Cancer Institute (<http://www.nci.nih.gov/>) (NCI) and Polyphenon E International for these initial clinical trials.

CLL is a blood cancer that is a hybrid between leukemia and lymphoma. Progression of the disease is measured by the quantity of leukemia cells in the blood and bone marrow as well as enlargement of lymph nodes due to infiltration by the leukemia cells. In the phase I study, published in May 2009 in the *Journal of Clinical Oncology*, researchers found that the blood lymphocyte (leukemia cell) count was reduced in one-third of participants, and that the majority of patients who entered the study with enlarged lymph nodes due to involvement by CLL saw a 50 percent or greater reduction in their lymph node size.

Using the highest dose tested in the phase I study, the researchers launched their phase II clinical trial in an additional 36 patients. The results presented at the ASCO meeting evaluate the effects in these 36 patients as well as the six patients from the phase I trial treated at the same dose (total 42 patients). Results from 41 patients who have completed the study show that 31 percent of patients had a 20 percent or greater sustained reduction in blood leukemia count, and 69 percent of patients with enlarged lymph nodes saw a reduction of node size of 50 percent or greater.

In all, 69 percent of CLL patients had a biological response to EGCG as evidenced by a 20 percent or greater sustained reduction in blood lymphocyte count and/or a 50 percent or greater reduction in lymph node size, the researchers say.

Because EGCG was being studied in patients who did not otherwise need treatment, the researchers took a

rigorous approach toward studying side effects. Most clinical trials of therapeutic agents only report grade 3 and higher side effects, but the researchers looked at and reported grade 1 and grade 2 as well. While a number of patients had transient grade 1 or 2 side effects, only three of 42 experienced a grade 3 side effect during their six months of treatment.

"All in all, the treatment was well tolerated with very mild side effects in most patients," Dr. Shanafelt says.

The researchers say that the prior publications on the effects of EGCG on CLL leukemia cells in the laboratory and the data from the published phase I study have been widely disseminated via the Internet by patient advocacy groups. Based on information from patients and colleagues throughout the country, the Mayo researchers have become aware that many CLL patients nationwide have started to use EGCG supplements, which are readily available over the counter.

"Without a phase III clinical trial, we cannot make a recommendation that EGCG be used by CLL patients, but those who want to take supplements should consult with their oncologists and need to receive appropriate monitoring using laboratory tests," Dr. Kay says.

Public release date: 7-Jun-2010

Blood-sugar lowering medications may increase risk for false positive results in cancer screenings

New study suggests that medication used to control blood sugar levels can distort results of some molecular imaging screenings for cancer

SALT LAKE CITY—A study presented at SNM's 57th Annual Meeting suggests that medication ingested to control blood-sugar levels can skew the results of cancer screenings using positron emission tomography (PET), a molecular imaging technique, by increasing absorption in the gut of the PET imaging agent called fluorodeoxyglucose (18F-FDG), which mimics sugar inside the body.

"The use of certain medications can influence where and how much of the imaging agent is taken up by the body," said Kyle Hurtgen, certified nuclear medicine technologist, Saint Louis University Hospital, St. Louis, Mo., and lead author of the study. "It is important for technologists to know the patient's history and use that information to their advantage to help physicians detect cancer and provide the best possible treatment for diabetic patients."

According to the study, diabetic patients taking tablet-form medications to help control blood-sugar levels prior to being screened for cancer using PET showed abnormally high intestinal absorption of 18F-FDG, a sign that normally indicates a cancerous tumor.

Suspiciously high absorption of this agent, which is bound with a molecular compound that acts like glucose and is metabolized by cells in the body as fuel, is seen as a "hot spot" on a PET scan. These hot spots can signal the high metabolic activity of cancer cells, but blood-sugar lowering medications called oral hypoglycemics can cause a similar visual effect that may make diagnosis more difficult. Determining the use of these medications and potentially discontinuing their use prior to imaging may improve diagnostic accuracy for diabetics, especially those suspected of having colon or other bowel cancers.

The study was conducted at Saint Louis University Hospital using advanced PET/CT technology. The research involved the imaging of three groups of patients with known or suspected extraabdominal cancer. Patients in one group had been diagnosed with diabetes mellitus and had taken oral hypoglycemics prior to imaging. Another group included diabetic patients who had not taken these medications and the third group included non-diabetic patients. More than 60 percent of those who had taken oral hypoglycemics were determined to have much higher bowel and intestinal uptake of the tracer than patients in the other two groups, prompting technologists and clinicians to carefully evaluate the use of blood-sugar lowering medications when imaging diabetic patients.

**These reports are done with the appreciation of all the Doctors, Scientist, and other Medical Researchers who sacrificed their time and effort. In order to give people the ability to empower themselves. Without the base aspirations for fame, or fortune.
Just honorable people, doing honorable things.**