A recent investigation by a US-based research group into the potential increase in risk of stroke with tamoxifen use has concluded that no such risk exists but there may be an increased risk with chemotherapy.

New research reveals no link between tamoxifen use and risk of stroke

Results from a trial involving 179 women with confirmed strokes after the diagnosis of breast cancer have revealed that there is no association between the use of tamoxifen and the development of stroke, however, it now appears that chemotherapy can more than double the risk of stroke in women.

The study, carried out by researchers at Kaiser Permanente (CA, USA), published in the October 20th issue of *J. Natl Cancer Inst.*, contradicts previous studies that demonstrated an increased risk of stroke with tamoxifen use, however, Ann Geiger, group leader with the study noted these trials did not control the data for the participants' other risk factors for stroke nor did they independently confirm the stroke diagnosis.

Geiger commented that "The bottom line from this study is when we looked at women who had a first stroke after their breast cancer diagnosis, we did not see a relationship between tamoxifen and stroke".

It has not yet been elucidated however why chemotherapy may contribute to an increase in the risk of stroke and Geiger was keen to stress "that the overall risk of stroke is very low compared to the known benefits of chemotherapy". The group have however suggested that women who have undertaken chemotherapy regimines were more likely to have suffered from more severe forms of cancer which would have contributed to an increased risk of stroke anyway.

Geiger also commented that the risk may be attributable to the fact that a number of the drugs administered to women to control some of the side effects of chemotherapy may also increase the risk of stroke. She continued "I think if women are considering tamoxifen, they and their clinicians probably don't need to be worried about stroke risk. Women who have had chemotherapy probably will want to manage their stroke risk as best they can by controlling blood pressure and cholesterol and watching their diet and exercising".

Jay Brooks, Chief of hematology/oncology at Ochsner Clinic Foundation Hospital (NY, USA) also noted "I think this study is reassuring for patients on tamoxifen, but it is in conflict with some of the other studies that found the risk of stroke in patients on tamoxifen is increased, but relatively low".

He also added that "I tend to shy away from tamoxifen in patients with an increased risk of cardiovascular disease because of the availability of other agents that prevent the return of breast cancer".

Ruth O'Regan, Director of translational breast cancer research at Emory University's Winship Cancer Center (GA, USA) has also commented on the findings of what she noted to be "a very good epidemiological group".

"I would consider this a 'real' finding regarding tamoxifen. And if you look at previous data, there is a slightly increased risk of stroke, but it's not as conclusive as other risks like [lung blood clots]." she continued.

Furthermore, O'Regan was surprised by the findings of an increased risk of stroke with chemotherapy and added "I'm not aware of any stroke increase with chemotherapy. But we must keep in mind this is one study, and this hasn't been shown before. I don't think you can make much of this".

Paul Tarter, Professor of surgery ar St Luke's Roosevelt Comprehensive Breast Breast Center and Columbia University College Physicians and Surgeons (NY, USA) also expressed his interest in the research findings and commented that "Patients should be relieved about tamoxifen". He added that "This rings with my clinical experience. I've got several thousand women in my practice and I rarely, rarely see a stroke. In fact, I don't remember ever seeing a stroke in someone taking tamoxifen".

Letrozole shown to reduce breast cancer recurrence

A team of breast cancer researchers from Manchester's Christie Hospital (UK) have reported exciting results with a drug designed to stop the disease recurring. Letrozole (Femara®, Novartis) was shown to reduce the likelihood of death in breast cancer patients by 39%.

Statistics show that one in nine women in the UK will develop breast cancer, with more than 1000 women dying from the disease every month. Currently, women with breast cancer undergo standard 5-year tamoxifen treatment. Researchers have shown that more than a third of sufferers will experience a relapse after surgery, with half of those relapses occurring after the 5 years of standard tamoxifen treatment. This trial from the Christie Hospital showed that letrozole can be prescribed after the standard treatment finishes and reduces the risk of recurrence by 42%.

Paul Ellis, leading cancer specialist and research spokesman noted "These results and the improved survival benefits are exciting for both patients and doctors."

Letrozole is now being made available to women with breast cancer who have undergone standard 5-year tamoxifen.

"This is a significant and welcome step forward for postmenopausal women who have finished their tamoxifen treatment for early breast cancer but are naturally concerned about recurrence," said Antonia Bunnin, Campaigns Director of charity Breakthrough Breast Cancer.

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Priority Paper Alerts

Developments in combination chemotherapy for colorectal cancer.
Goetz MP, Grothey A. *Expert Rev. Anticancer Ther.* 4(4), 627–637 (2004).
Examines developments in the field of chemotherapy for colorectal cancer from the domination of the field by 5-flourouracil for over 30 years to the emergence during the past 5 years of newer drugs such as irinotecan (Campto®, Aventis) and oxaliplatin (Eloxatin®, Sanofi-Synthelabo). Furthermore, studies of the use of combination chemotherapy drugs with biologic agents that target angiogenesis and tumor growth pathways are reviewed.

Safety of rosuvastatin.
Shepherd J, Hunninghake DB, Stein EA *et al. Am. J. Cardiol.* 94(7), 882–888 (2004).
Describes the results of a multinational Phase II/III program to assess the safety and tolerability of rosuvastatin (Crestor®, AstraZeneca) in a population of 12,400 patients who received 5 to 40 mg of the drug. Results demonstrated that the drug is well tolerated over a broad range of patients with dyslipidemia and that the safety profile is similar to that of other statins used in the investigations.

Comparative effects of statin and fibrate on nitric oxide bioactivity and matrix metalloproteinase in hyperlipidemia.
Koh KK, Ahn JY, Jin DK *et al. Int. J. Cardiol.* 97(2), 239–244 (2004).
Examination of the lipoprotein effects of statin and fibric acid derivative therapies in patients with hyperlipidemia on lipoproteins, vasomotor function and plaque stability using a 20 mg daily dose of simvastatin on 27 patients with hypercholesterolemia and coronary artery disease and a 200 mg daily dose of fenofibrate on 27 patients with pure hypertriglyceridemia over an 8-week period. The study confirmed that simvastatin and fenofibrate exhibit atherosclerotic effects via different mechanisms.

Aspiration of dead space in the management of chronic obstructive pulmonary disease patients with respiratory failure.
Liu YN, Zhao WG, Xie LX *et al. Respir. Care* 49(3), 257–262 (2004).
Examination into whether the use of aspiration of dead space would allow for lower tidal volume and potentially reduce exposure to ariway pressures in a population of eight hemodynamically stable, normothermic, ventilated patients who suffer from severe chronic obstructive pulmonary disease. Results demonstrated that the procedure can decrease levels during mechanical ventilation and permissive hypercapnia.

New promise of human gene therapy for erectile dysfunction

Preliminary results from an early test of human gene therapy for erectile dysfunction announced recently at the Meeting of the International Society for Sexual and Impotence Research have reported no treatment-related side effects in any of the first three patients involved.

The trial, being carried out at Mount Sinai School of Medicine (NY, USA) under the auspicies of Dr Albert Melman, is currently examining the safety of a single penile injection of a gene called maxi-K, which is involved in diminishing smooth muscle contraction, eventually leading to relaxation and erection.

Following on from this early success, plans are currently underway to recruit and test a further six patients by the end of the year, with the aim of commencing efficacy trials by the end of 2005. Melman is confident that therapy may become commercially available "within the next 7 to 8 years".

"In the best case, the method will work by itself. On the other hand, you might be able to use lower doses of Viagra® (sildenafil, Pfizer), Cialis® (tadalafil, Lilly ICOS) or Levitra® (vardenafil, GlaxoSimthKine) or improve their efficacy" Melman continued. He also added that "If it works, it will be revolutionary".

It is currently estimated that a single dose of the therapy will cost around US$400, and that there may be a need for booster injections every 6 months.

Genetic link found between heart disease and Type 2 diabetes

Results of a study carried out by researchers at the Joslin Diabetes Center (MA, USA) have identified a gene that could help to explain the link between patients with Type II diabetes and coronary artery disease.

It is currently estimated that up to 18 million people in the USA are diagnosed with Type 2 diabetes and that this group of the population are two to four times more likely to develop cardiovascular disease. The current study focused on a gene that governs that CD36 protein which is found in the membrane of numerous cell types, but most interestingly, in the walls of blood vessels. It has been demonstrated previously that CD36 is, amongst other things, involved in transporting free fatty acids into cells, as well as being a scavenger of oxidized low-density lipoprotein cholesterol at the site of the arterial wall.

Alessandro Doria, an investigator with the group, has commented on the findings "We now have potential gene markers to help identify diabetes patients at increased risk for heart disease". He continued that "This knowledge could potentially lead to drugs or other methods that affect this pathway, reducing the risk of heart attack and stroke in these patients".

"While this research is a significant starting point for assessing risk of heart disease, a constellation of factors are involved," said Doria. "But it is clear that in addition to high blood pressure, high cholesterol and environmental factors such as smoking, genes are important determinants of heart disease in people with Type 2 diabetes."

Gene variant discovered which may help protect against developing asthma

A report in a recent issue of the *N. Engl. J. Med.* by a group at the Brigham and Women's Hospital has described the discovery of a new gene variant that, when present in a person, decreases the risk of developing asthma.

Results from a study carried out at the Brigham and Women's Hospital in Boston (MA, USA) have identified a form of a gene that prevents the development of asthma in carriers.

The gene variant, which carries the prostaglandin (PTG) receptor, PTGDR, when absent in an individual, does not automatically predispose the carrier to developing the breathing disorder, but is thought to be an indicator that the disease may develop.

Speaking of the study, Craig Lilly, Director of the Medical Intensive Care unit at the hospital commented that "This is the first gene that's been described that protects people from asthma". The present study was prompted by previous investigations which had indentified a region of the human genome that was thought to contain asthma susceptibility genes. Lilly noted that "There were a lot of other studies that indicated something in this region that made people susceptible".

As part of the study, the group examined variants in the genes of 518 white and 80 black subjects and compared the results against those from 175 white and 45 black individuals who did not suffer from asthma. The results concluded that those with asthma were approximately half as likely to possess the gene variant.

Lilly commented further that there are now a number of PTGDR blockers ready to enter clinical trials.

However, Jonathan Field, Director of the pediatric allergy immunology clinic at New York /Bellevue Hospital (NY, USA) has stressed that this does not necessarily translate to a definite cure for asthma "This is one potential site in the spectrum of asthma, one potential area that may be linked to the severity of asthma". He continued "The goal with scientists and clinicians is to use this information and temper it with clinical evidence from patients and continue doing studies with it in large populations."

Biogen Idec's alefacept (Amevive®) is approved for use in Canada for the treatment of psoriasis

It was announced on the 14th October that Health Canada has approved the countries first biologic, alefacept (Amevive®, Biogen Idec.), for the treatment of moderate-to-severe chronic plaque-type psoriasis in patients who are candidates for systemic or phototherapy.

Alefacept, a T-cell inhibiting, CD2 antagonist, LFA3–immunoglobulin(Ig)G1 fusion protein for the treatment of psoriasis, was previously approved in the USA in February, 2003, at which time it became the first biologic therapy to be approved for the treatment of moderate-to-severe chronic plaque-type psoriasis in adults.

Alefacept is also currently under development by the company as a potential treatment option for other autoimmune disorders such as psoriatic and rheumatoid arthritis, with Phase II trials for rheumatoid arthritis having been initiated in December 2000.

Biogen Inc. was recently merged with IDEC Pharmaceuticals Corp. to form Biogen Idec Inc., which is invloved in the development, manufacture and commercialization of novel therapies.

Announcement of promising new 2-year TEMPO study results

Promising new 2-year results from the ongoing Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study have been presented recently at the American College of Rheumatology's Annual Scientific Meeting (TX, USA).

Reports from the conference have revealed that nearly 74.2% of patients with rheumatoid arthritis (RA) treated with etanercept (Enbrel®, Amgen) plus methotrexate in combination therapy over a 2-year period, experienced no progression in joint damage during that time.

Speaking at the conference, Desiree van der Heijde, Professor of rheumatology at the University of Maastricht (The Netherlands) commented "It is remarkable to see that a large majority of patients experienced no progression of joint damage while on Enbrel and methotrexate combination therapy. Moreover, the patients taking the combination therapy had better mean x-ray scores as a group after two years compared to baseline." He continued that "These data confirm the 1-year results and underscore the importance of aggressive treatment to help prevent long-term disability."

For further information on etanercept, see Fleischmann R, Stern R & Iqbal I. Etanercept – a review of efficacy and safety after five years of clincal use. *Therapy* 1(1), 11–23 (2004). Available now at www.future-drugs.com

Ximelagatran (Exanta™) is rejected by the US FDA for use as an oral anticoagulant

Ximelegatran (Exanta™) has recently been rejected by the US FDA for use as an oral antocoagulant following a number of safety concerns.

An advisory panel of the US Food and Drug Administration (FDA) has rejected ximelagatran for use as an oral anticoagulant. The drug is produced under the name Exanta™ by AstraZeneca, who requested the following three-part indication: prevention of venous thromboembolism in patients undergoing knee replacement surgery; prevention of stroke and other thromboembolic complications associated with atrial fibrillation; and long-term secondary prevention of venous thromboembolism after standard treatment of an episode of acute venous thromboembolism.

The company suggested that ximelagatran could be an alternative to warfarin based on the results of a number of trials including the THRombin Inhibitor in Venous Embolism (THRIVE) III trial, the EXanta Used to Lessen Thrombosis (EXULT) A and B trials, and the Stroke Prevention using the ORal direct Thrombin Inhibitor ximelagatran in patients with nonvalvular atrial Fibrillation (SPORTIF) III and V trials.

Vice President of Exanta at AstraZeneca, Hamish Cameron, said, "Ximelagatran provides predictable kinetics and dynamics allowing fixed dosing, there is no need for anticoagulation monitoring, there is a low risk of food and drug interactions, there is a rapid onset of action, and there is an acceptable bleeding profile." However, the advisory panel had concerns over the safety of the drug, with patients having an approximately one in 2000 chance of developing liver failure.

Steven E Nissen, Vice Chairman of the department of cardiology at the Cleveland Clinic Foundation, commented that this risk was too high "I'm troubled by the nature of this liver injury in that it is difficult to predict. My judgement from hearing the cases is that it is almost certainly drug related" said Nissen.

A member of the panel, Jeffrey S Borer, chief of the division of cardiovascular pathophysiology at Weill Medical College of Cornell University, agrees with this, but believes that the benefits of the drug should also be considered.

"It's hard for me to talk about safety without putting it in the context of benefit. Having an alternative would be very attractive. The risk may be one in 2000, but to prevent a major event you only have to treat 15 patients, so this has to be considered," said Borer.

New study reveals a number of potential benefits associated with long-term oral contraceptive use

Results from the largest study into the long-term consequences of oral contraceptive use published recently by researchers from Wayne State University (MI, USA) have shown that long-term use appears to play a role in preventing heart disease and some cancers in women. Results of the study, which compared over 60,000 women with had a history of oral contraceptive use with a group who had no history, were presented at the *Annual Conference of the American Society for Reproductive Medicine* (PA, USA).

The study found that women who used oral contraceptives for a duration of between 1 and 4 years then had a 10% lower risk of developing cardiovascular illnesses such as heart attacks, hypertension and angina. Whereas those who used contraceptives for 4 to 8 years had an 18% lower risk. It was also noted that users of oral contraceptives had a 7% lower risk of developing cancers.

Speaking of the findings, Raho Victory, the chief author of the study, commented "In stark contrast to recent and previous findings, our data supports significant cardiovascular disease risk reductions in women with a history of oral contraceptive use. In women with no other risk factors [such as family history of heart disease], the Pill could be used to prevent cardiovascular events and some cancers".

He also commented that data from previous studies that found adverse effects associated with long-term oral contraceptive use was "flawed".

Comment was also provided by Ann Furedi, Chief Executive of the British Pregnancy Advisory Service and she noted that "Given that so many women do use the Pill ... any study that shows health benefits above and beyond its excellent record on preventing pregnancy is to be welcomed. Women worry that the benefit of preventing unwanted pregnancies is bought at the cost of a long-term health risk, so this is very reassuring."

While it is thought that the anticancer effect is due to the presence of estrogen hormones in oral contraceptives, further research is needed to discover the exact mechanism of protection.