

## Bird flu (avian influenza)

Influenza viruses are known to infect birds and animals, mostly pigs and horses. Avian influenza viruses do not usually infect humans. Nevertheless, in May 1997 in Hong Kong 18 human cases of influenza caused by bird-to-human transmission of AH5N1 avian influenza occurred with six deaths. Since 2003, this highly pathogenic AH5N1 virus has spread rapidly to poultry in 17 countries in Asia and Eastern Europe. Most of the resulting 118 human cases have been healthy young children or adults in close contact with infected flocks, with over 50% mortality.

Although this AH5N1 virus does not currently have the capacity to cause a human pandemic, there is potential for antigenic shift, either from a gradual process of adaptive genetic mutation within the virus or by snap gene reassignment with a human influenza A virus. The virus could acquire the mechanism for rapid human transmission and cause explosive global spread as has happened in the past; “Spanish” flu in 1918–9, “Asian” flu in 1957–8 and “Hong Kong” flu in 1968–9.

Pigs and humans seem to be the “mixing vessels” for genetic exchange when co-infected by both animal and human influenza viruses. Exchange is facilitated by close domestic proximity of fowl, pigs and humans as commonly found in Asia. *British Medical Journal* 2005; **331**: 975–6.

## Nobel Prize 2005, in physiology or medicine

Two Australian researchers, Barry Marshall and Robin Warren were chosen as winners of the 2005 Nobel Prize in physiology or medicine. Professor Marshall 54, and Dr. Warren 68, are cited for their 1982 discovery of “the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease”.

As a clinical pathologist at the Royal Perth Hospital, Dr. Warren noticed a parallel between the severity of inflammation and bacterial presence in stomach biopsy specimens. He worked with Professor Marshall, at that time a trainee doctor in the same hospital, to show a causal connection between the two observations.

Culturing bacteria from stomach specimens was initially unsuccessful. An unintentional longer incubation of the culture plates allowed a flourishing growth of *H. pylori*.

To answer the question whether the organism caused inflammation or whether the inflammation allowed *H. pylori* to grow, Marshall swallowed a culture of bacteria, developed gastritis, and *H. pylori* was demonstrated in his stomach biopsy. *British Medical Journal* 2005; **331**: 646–7.

## Prevention of rabies

Rabies is an acute, incurable, viral encephalomyelitis caused by a bullet shaped RNA rhabdovirus. The incubation period is variable, but is typically from 1 to 3 months. Since rabies cannot be cured, prevention and prophylaxis are vital.

Vaccination before exposure simplifies treatment and provides protection after unrecognised exposure. Currently available rabies vaccines containing inactivated virus derived through tissue culture are safe and effective. For prophylaxis before exposure, three doses of vaccine are given into the deltoid muscle on days 0, 3 and 28, and boosters can be given between 6 and 24 months. Prophylaxis after exposure aims to neutralise the virus before it can enter the nervous system. Methods available for post-exposure prophylaxis include wound cleaning, passive immunisation with immunoglobulin, and active immunisation with vaccine.

Wound care is essential to prevent rabies infection. The wound needs to be thoroughly scrubbed with soap and water or, if available, iodine solution, 40–70% alcohol, cetrimide 0.1%, or the viricidal agent povidone. Wound cleaning should be done under local anaesthesia where appropriate. The rabies virus is killed by sunlight, drying, soap or the agents mentioned. In animal experiments, early effective wound cleaning has been shown to prevent rabies infection. For travellers to endemic regions, particularly to remote rural areas, making a decision on pre-exposure vaccination requires an assessment of the risk of being bitten and local access to safe and effective rabies immunoglobulin and vaccines. *British Medical Journal* 2005; **331**: 469–70.

## Pre-natal and post-natal growth and adult health outcomes

Evidence indicates that exposure to stress and toxins in the pre-natal period, feeding and rate of growth during infancy and childhood may influence the occurrence of chronic diseases as an adult. Researchers have found consistent inverse associations between birthweight and a central distribution of body fat, insulin resistance, the metabolic syndrome, type 2 diabetes mellitus and ischaemic cardiovascular disease. Lower birthweight coupled with a higher body mass index in childhood or adulthood is associated with the highest risk of such outcomes.

A new generation of epidemiologic studies directly examines the effects of pre-natal determinants and post-natal health outcomes irrespective of birthweight. These studies have shown that maternal under-nutrition, a well known cause of low birthweight, includes not only maternal diet but also uteroplacental blood flow, placental function and fetal metabolism.

Experience in animals shows that reduced activity of the placental enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 2, resulting from excess fetal exposure to glucocorticoids, increases the risk of hypertension and hyperglycaemia in the offspring. Gestational diabetes (which is associated with higher birthweight) leads to fetal hyperinsulinaemia, obesity and impaired glucose tolerance in the growing child. In populations undergoing transition to western styles of diet, sedentary behaviour, obesity and chronic diseases, low birthweight and weight gain in childhood are both common.

In addition to optimising childhood growth, researchers and policymakers should identify and quantify pre-natal and peri-natal determinants of chronic diseases in adults and evaluate strategies to modify these determinants. Investigators in the field of “developmental origins of health and disease” are slowly but surely learning ways of ensuring the well-being of women of reproductive age and their newborn children. This is likely to cause substantial health promoting effects in the next generation. *New England Journal of Medicine* 2005; **353**: 1848–50

### Angio-oedema with angiotensin converting enzyme inhibitors

Of over 7000 reports of angio-oedema received by the Adverse Drug Reactions Advisory Committee in Australia since 1970, ACE inhibitors account for 12.6%.

Angio-oedema may present with acute onset soft tissue swelling of the face, tongue, pharynx and neck. Rarely, oedema of the gastrointestinal tract may cause episodes of abdominal pain, vomiting and diarrhoea. Acute onset angio-oedema requires prompt parenteral administration of adrenaline if the airway is compromised. The first occurrence of angio-oedema may occur after months or even years of ACE inhibitor therapy. It may also occur episodically with long symptom free intervals.

Angio-oedema is thought to be associated with potentiation of bradykinin, causing increased vascular permeability and vasodilation. Angiotensin II antagonists also cause angio-oedema. Individuals with a history of angio-oedema with ACE inhibitors may occasionally get it with angiotensin II antagonists as well. *WHO Drug Information* 2005; **19**: 116–7

### Digital mammographic screening

Digital mammography is a film-less technique of mammography that permits the elimination of film processing, storage, copying and retrieval. Digital image manipulation makes it possible to place images in a window, level them, and electronically magnify them. Other advantages of digital imaging are real-time interpretation of mammograms at distant sites with the use of teleradiology and computer aided detection equipment. These advantages must be weighed against the cost of digital imaging systems which are up to four times as expensive as film mammography systems.

Three previously published reports have shown film mammography to be similar to or better than digital mammography. Results of a recent study (Digital Mammographic Screening Trial) suggest that digital mammography has significant advantages in some sub-groups of women, although data for the entire population show no advantage of one technique over the other. In this study digital mammography had a significant advantage among women who were younger than 50 years of age, women who were premenopausal or perimenopausal, and those with radiographically dense breast tissue on film mammography.

The most important message given by the work of several researchers in the field is that good quality screening mammography saves lives. The availability of high quality images, skilled interpretation, and the screening of all women who are eligible for it give optimum benefit. All women 40 years or older should be screened. When both types of equipment are available, the decision to use digital or film equipment should be tailored to the individual woman. If only one type of equipment is available, women should realise that most of the benefit of mammographic screening is derived from the test itself and not from the way the image is stored. *New England Journal of Medicine* 2005; **353**: 1846–7.

### New treatment for breast cancer

Recent research has shown the efficacy of a monoclonal antibody, trastuzumab in the treatment of primary breast cancer, as measured by reduction in the rates of recurrence and death.

The human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGFR) family of transmembrane tyrosine kinases, and is normally involved in the regulation of cell proliferation. The HER2 gene is located on the short arm of chromosome 17. The HER2 gene, discovered in 1983, was found to be related to the EGFR.

Amplification (an excess number of gene copies) of the HER2 gene or over expression (excess production of protein) of the gene on the affected cancer cells, indicate enhanced growth and proliferation, increased invasive and metastatic capability, and stimulation of angiogenesis. It was observed that a monoclonal antibody against the EGFR inhibited binding of the natural ligand (EGF) to the receptor and inhibited receptor phosphorylation and signalling. Based on this researchers developed a mouse monoclonal antibody with high affinity for the HER2 transmembrane protein. A molecularly engineered humanised version of this antibody is trastuzumab.

Four large multi-centre trials were designed to test the role of trastuzumab as adjuvant therapy after surgical treatment of primary breast cancer. The results of three of these studies are stunning. With 12 to 30 months' follow up, all three trials show highly significant reduction in the risk of recurrence, of a magnitude seldom observed in oncology trials.

These results compelled the respective data and safety monitoring committees to stop the trials after the first interim analyses. Trastuzumab was offered to patients in the control groups. On the basis of these results, lymph node positive, HER2 positive breast cancer patients should receive trastuzumab as part of optimal adjuvant systemic therapy. Patients with negative lymph nodes should also be offered the antibody after weighing the risks of recurrence and the risk of cardiotoxicity with trastuzumab.

Clearly, the results of these trials are not evolutionary, but revolutionary. The rational development of molecularly targeted therapies points the direction towards continued improvement in breast cancer therapy. *New England Journal of Medicine* 2005; **353**: 1734–6.

### **New kidney function test**

Cystatin-C, a new blood test for kidney function, is a better predictor of death and cardiovascular risk among the elderly than the standard measures of kidney function. A recent study compared the two measures of kidney function, cystatin-c and the standard test serum creatinine, among 4637 elderly participants.

The 20% participants with the highest levels of cystatin-C had twice the risk of death from all causes as well as death from cardiovascular disease and a 50% higher risk of heart attack and stroke compared with those who had the lowest levels of cystatin-C. In contrast, testing the same participants with serum creatinine detected a high risk only in 10% of the participants. With cystatin-C investigators found that 60% had abnormal kidney function putting them at medium or high risk for cardiovascular complications. Cystatin-C is FDA approved for diagnostic use, but the test is not yet widely available. *WHO Drug Information* 2005; **19**: 115.

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## **Principle of beneficence in research**

The principle of beneficence, widely recognised as one of the fundamental principles of research ethics, entails an obligation to provide an established, effective treatment to a control group in a clinical trial regardless of whether the treatment is routinely available in the host country.

Draft document, US National Bioethics Advisory Committee.