after Fontan’s procedure, who also developed ascites and pleural effusions. The circulation of these patients is hampered by increased central venous pressure due to the absent right ventricle.\(^2\) Patients with effusive complications after Fontan’s procedure had a decreased peripheral resistance (1486 vs 2687 dyn cm\(^{-1}\) m\(^{2}\)) and an increased cardiac output (3.6 vs 2.4 L min\(^{-1}\) m\(^{2}\)) compared with patients without effusions. The mechanism involved seems to be an increased mean capillary filtration pressure,\(^1\) calculated from this haemodynamic data (24.3 vs 18.3 mm Hg) by an algorithm based on Starling’s theories of ultrafiltration in the capillaries.

Since patients were resistant to diuretic therapy, we treated three patients with propranolol to decrease the cardiac index and increase peripheral resistance. All patients improved clinically and the effusions resolved. With clinical improvement, we observed a decrease in plasma renin and aldosterone concentrations. Thus \(\beta\)-blocker therapy seems to influence the mean capillary filtration pressure, with the additional benefit of inhibition of renin release via \(\beta\)-receptor blockade.

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**CORRESPONDENCE**

**Nitric oxide and response to inhaled bradykinin in severe asthma**

Sir—Fabio Ricciardolo and co-workers (Nov 1, p 1297)\(^1\) describe the response to inhaled bradykinin in ten patients with severe asthma. The patients had a forced expiratory volume in 1 s (FEV\(_1\)) of 65–75% and were on inhaled corticosteroids. The dose of inhaled corticosteroid was not stated, so whether they had severe as opposed to moderate asthma is uncertain. The ten patients had a greater response to inhaled bradykinin than individuals with mild asthma (who were not on treatment with inhaled steroids) and unlike the mild asthmatics the patients’ response to bradykinin was not potentiated by L-NMMA, a nitric-oxide-synthase inhibitor. Ricciardolo and colleagues conclude that in severe asthmatics there was a loss of the bronchoprotective effect of the nitric oxide formed in the airways by the constitutive form of nitric-oxide synthase. Their findings could also be explained by inhaled corticosteroids blocking the formation of nitric oxide by the inducible form of nitric-oxide synthase (iNOS). We believe that the latter explanation is more likely.

We compared the response to inhaled bradykinin in eight mild asthmatics and ten patients with severe asthma. Subjects with mild asthma had an FEV\(_1\) greater than 80% of predicted (mean 54.1% predicted) and inhaled steroid dose of >1600 µg daily (mean 1960 µg) of beclomethasone dipropionate. The severe asthmatics had an FEV\(_1\) less than 80% of predicted (mean 41.5% predicted) and inhaled steroid dose of >1600 µg daily (mean 1690 µg) of budesonide or fluticasone propionate. Doubling concentrations of bradykinin were inhaled until there was a 20% fall in FEV\(_1\) (PC\(_{20}\) FEV\(_1\)) or inhaled steroid dose of 0–400 µg daily (mean 250 µg) of beclomethasone dipropionate. The severe asthmatics had an FEV\(_1\) greater than 80% of predicted (mean 54.1% predicted) and inhaled steroid dose of >1600 µg daily (mean 1960 µg) of beclomethasone dipropionate. The geometric mean PC\(_{20}\) for bradykinin was 0.027 mg/mL for the mild asthmatics and 1.71 mg/mL for the severe asthmatics (p<0.005).

To investigate whether the reduced response to inhaled bradykinin in severe asthmatics was due to the formation of nitric oxide we conducted a double-blind crossover study of the effects of nebulised L-NMMA. A geometric mean PC\(_{20}\) for bradykinin was 0.027 mg/mL with saline and >1600 µg daily (mean 1960 µg) of budesonide or fluticasone propionate. Doubling concentrations of bradykinin were inhaled until there was a 20% fall in FEV\(_1\) (PC\(_{20}\) FEV\(_1\)) or a concentration of 8 mg/mL was reached (in which case the PC 20 was reached). The geometric mean PC\(_{20}\) for bradykinin was 2.92 mg/mL with saline on the response to inhaled bradykinin in patients with severe asthma. The latter explanation is more likely.

We believe that inhaled bradykinin seen in the patients described by Ricciardolo and co-workers reflects the ability of inhaled steroids to suppress the formation of nitric oxide by iNOS in the airways of mild to moderate asthmatics. By contrast, in our group of severe asthmatics, the reduced response to bradykinin results, at least in part, from the formation of nitric oxide in the airways, an effect which is not abolished by treatment with high doses of inhaled steroids.

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**Authors’ reply**

Sir—In view of Peter Black and Susanne Brodie’s results in severe asthmatic patients treated with high doses of steroids, the issue of nitric oxide (NO) production in asthma needs further clarification. They postulate that the moderate bronchoconstriction they recorded in their patients is due to increased formation of NO from the inducible form of NOS (iNOS), with no effect of high-dose of inhaled steroids. Furthermore, they speculate that our results can be explained by the ability of steroids to suppress NO formation by iNOS within the airways of asthmatics with less severe disease.

This was one possible explanation, but others cannot be discarded by current data. First, steroids may influence bronchial responsiveness independently from NO release. Thus, the high doses of steroids in Black and Brodie’s study could have reduced the response to bradykinin per se, as has been reported in a study in which bronchial responsiveness to methacholine, a bronchoconstrictor that is marginally affected by NO release,\(^1\) was reduced by steroid therapy.

Second, two functionally distinct isoforms of NOS—constitutive (cNOS) and iNOS—have been described in the airways. cNOS stimulation via a rapid increase in the intracellular calcium concentration results in the rapid (s or min) release of pmol of NO. By contrast, the expression of iNOS is induced by proinflammatory cytokines, such as tumour necrosis factor-\(\alpha\), interferon-\(\gamma\), and interleukin-1\(\beta\), and results in the release of nmol of NO several hours after cytokine exposure, an effect that may continue for days and that is inhibited by steroids.\(^3\)
There is indirect evidence that the bronchorelaxant NO released by bradykinin derives from cNOS. In chronic asthma increased expression of the epithelial isoform of CD44 suggests that the epithelium transforms into a repair phenotype expressing a range of bioactive molecules, including cytokines, growth factors, and iNOS. Chronic inflammatory factors in severe asthma, including high level of NO, may suppress cNOS activity, and high doses of inhaled steroids could reactivate the formation of bronchoprotective NO.

The hypothesis that we discussed and that is favoured by Black and Brodie cannot be accepted until evidence is provided that bradykinin rapidly (α or min) stimulates the release of bronchorelaxant NO from airway iNOS and that NO inhibitors fail to increase bronchial responsiveness to bradykinin in mild asthmatic patients not on steroid therapy or in healthy individuals, in all of whom, presumably, iNOS induction is minimum.

Existing evidence seems to disprove this hypothesis. In mild asthmatic patients off steroid therapy L-NMMA enhanced PC25FEV1, to inhaled bradykinin. In naive guinea-pigs bronchoconstriction to bradykinin and histamine was increased by iNOS inhibitors, and viral infection reduced the ability of histamine to release bronchorelaxant NO. Thus, we cannot reject the hypothesis that in severe asthma release of bronchoprotective NO from cNOS is inhibited, and that this mechanism might be partly responsible for hyperresponsiveness to bradykinin in asthma.

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### Terathanaemia, folic acid, and birth defects

**SIR**—After the Nov 1 correspondence debate on terathanaemia (p 1322), I would like to present our hypothesis. We appreciated the breakthrough in the primary prevention of neural-tube defects by folic-acid-containing multivitamin or folic-acid supplementation, but it is necessary to know all other possible effects of this method.

The final database of the Hungarian trial showed an increasing trend in the rate of fetal death including chemical pregnancies, miscarriages, and stillbirths. I agree to analyse the database with the introduction of the hypothesis of terathanaemia. However, my hypothesis for this mild increase of fetal death was based on the improved fertility and the significant increase (about 40%) in the rate of multiple pregnancies. There were three twins among 11 stillborn fetuses in the study group, compared with no twin in the nine stillborn fetuses in the placebo group. This increased rate of multiple birth after multivitamin supplementation was confirmed by a recent US study. Deficiency of folate or vitamin B12 may cause sterility which is reversible with appropriate vitamin supplementation. However, subfertile couples after the achievement of a pregnancy due to medical treatment have a somewhat higher rate of fetal death and low birthweight newborn babies. Thus, this secondary effect may explain the higher rate of fetal death.

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### Transmission of blood-borne viruses after motor- car accidents

**SIR**—Andrea Brambilla and colleagues (Nov 8, p 1370) report transmission of HIV-1 and hepatitis B virus infection (HBV) resulting from a head-buttng incident after a motor-car accident. In 1996 we dealt with an incident in which eight members of the emergency services and two members of the public were exposed to blood from a casualty at a road-traffic accident who was antibody positive for hepatitis C virus (HCV).

At the scene of the accident, the police had notified the paramedics that the injured person was hepatitis B surface antibody negative. This hypothesis was partly responsible for hyperresponsiveness to bradykinin in asthma.

When the patient arrived at the hospital, he denied having any known blood-borne virus infection. However, the patient died from severe head injuries 2 weeks later and the hospital health-care team wanted to investigate the possibility of occupational exposure to HIV-1, HBV, and HCV. The next day, ambulance staff reported to their various general practitioners that they had been exposed to HBV. The physicians contacted their local Public Health Laboratory for advice, but since they did not know the name of the injured person, who subsequently died, it was difficult to establish the true risk of blood-borne virus. The police were unwilling to reveal the name of the deceased to the virologist, and it took 1 h to locate the whereabouts of the body. It then took 1 h to obtain permission from the coroner to carry out tests for HIV, HBV, and HCV. Eventually, 7 h after the virologist was first notified, the dead person was found to be HIV-antibody negative, HBsAg negative, and HCV antibody positive. Nine contacts were followed up after the accident and 6 months later none were shown to be HCV antibody positive.

Several points emerge from this incident. Rapid determination of the blood-borne viral risk is essential to give prompt and appropriate postexposure prophylaxis for HBV or HIV-1. Occupational health services are mostly service-specific and often unavailable outside office hours, which leads to potential delay and conflicting advice. Most health districts have a consultant in communicable disease. The communicable disease control (CCDC) or deputy who are available at all times, liaise with clinical microbiology and public health laboratories, and make risk assessments together with microbiologists and virologists. They often have contacts with emergency services as a result of responsibilities for postexposure planning.

After this incident, our local police force produced a procedure for contacting the CCDC when there is concern about an infectious agent in