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Intergenerational expansion of CTG repeat length.

Parental expansion is expressed in no of CTG repeats, in which 500 repeats correspond to a 1.5 kb expansion. Regression lines A = mother-child pairs (+, n = 89); B = father-child pairs (■, n = 95).

spermatozoa bearing smaller repeats. This regression of the CTG repeat length may be the main cause of the longevity of DM alleles in the population, as evidenced by the strength of the linkage disequilibrium seen between genetic markers which map very close to the CTG repeat and DM.¹ The sex difference in the frequency at which contraction occurs may well be a major contributing factor to explain why the congenital form of DM is only inherited maternally. This difference, coupled with the decreased fertility of men bearing large amplifications, may explain this finding.

The case in which congenital DM is inherited despite a 3 kb contraction on transmission from mother to son has important implications for presymptomatic and antenatal diagnosis of DM, since until this case, it was assumed that a contraction on transmission would correspond to a decrease in the severity of the phenotype.²⁻⁵

Unitat de Genètica Molecular,
Hospital de la Santa Creu i,
Sant Pau,
Barcelona 08025, Spain

Department of Neurology,
Hospital Ntra Sra de Aránzazu,
San Sebastian

Department of Anatomy,
Charing Cross and Westminster
Medical School,
London W6, UK

A. M. COBO
M. BAIGET

A. LÓPEZ DE MUNAIN
J. J. POZA
J. I. EMPARANZA

KEITH JOHNSON

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Bacterial identification of adult lower respiratory tract infection

SIR,—Dr Macfarlane and colleagues (Feb 27, p 511) draw attention to community-acquired lower respiratory tract infection (LRTI). We take issue with most of their conclusions, since their methodology is inadequate. Their finding that most identified cases were diagnosed as having a bacterial infection does not imply genuine cause and effect. Previous studies in wheezing illness have shown that bacterial identification rates are the same whether the subjects were wheezy or symptom-free,¹ with up to 24% of symptom-free cases being positive on bacterial culture.² In

Macfarlane's study bacterial cultures were not obtained in healthy subjects nor in patients when they were symptom-free, and thus the significance of a positive culture is unclear.

Viral shedding is greatest within 1 day of symptoms and since symptoms had been present for at least 7 days in 67% of the cases, it is hardly surprising that the virus isolation rate (not precisely specified in the paper) was so low. Even with better clinical sampling techniques than those used, the use of "standard laboratory methods" is not adequate to identify most respiratory viruses. Respiratory viruses are notoriously difficult to culture, especially coronavirus and rhinovirus, which need very specialised culture conditions.² Nasal aspirate or washing offers greater sensitivity for respiratory viral culture.³ Likewise, serological testing is insensitive for respiratory viral diagnosis. It cannot identify rhinovirus, nor, without specialised techniques, coronavirus, and in Macfarlane's study parainfluenza was not sought. Together these viruses probably account for over three-quarters of respiratory viral infections.⁴

These deficiencies are underscored by a recent community-based longitudinal study in school children with persistent lower respiratory tract symptoms which used the polymerase chain reaction together with more traditional diagnostic methods. Respiratory virus infections were identified in 81% of wheezing episodes and in 83% of episodes with both upper and lower respiratory tract symptoms and a fall in peak flow—the identification rate in the same children when symptom-free was 12%.⁴ We estimate that had this study used the same methodology as Macfarlane et al the identification rate would have been 11% and the researchers would have erroneously concluded that viruses are unimportant in wheezing episodes in children.

Despite these shortcomings, the study has been successful in identifying the scale of LRTI in the UK, but has advanced us no nearer to identifying the causes. In particular, the place of antibiotic therapy should remain open to question since, despite treatment with antibiotics, 26% of patients in Macfarlane's study asked to see their general practitioners again because of unsatisfactory clinical progress. Although the polymerase chain reaction for virus identification was presumably not available when this study was planned, in any future investigations this technique must be used.

University Medicine,
Southampton General Hospital,
Southampton SO9 4XY, UK

IOLO DOULL
SEBASTIAN JOHNSTON

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Authors' reply

SIR,—We accept that present methods for diagnosing the pathogen causing LRTI are not wholly satisfactory, but our conclusion that the range of causative pathogens identified in our patients with such infection is similar to that for community-acquired pneumonia remains valid since our previous studies and those of others have used similar diagnostic techniques. We clearly stated our criteria for diagnosis of infection, which were similar to those in previous studies, including those used in the British Thoracic Society study.¹ Dr Doull and Dr Johnston's criticisms mainly relate to the diagnosis of viral infections. However, our study was of LRTI in general practice and not of wheezing illness in childhood and adult asthmatics referred to in their references. We agree that viral shedding is greatest at the start of symptoms, but we are uncertain how they suggest we could exploit this fact when studying a large unselected population who only seek help because of continuing symptoms. We are also uncertain how we could have had access to the elegant methods that Doull and Johnston describe in a twelve author, unpublished paper due to come out in a European Journal.

Doull and Johnston question the relevance of a positive bacterial diagnosis, and indeed this is a difficulty, but they do not suggest a practical alternative. The reference they cite of bacterial infection in asthmatics² failed to identify any cases of *Streptococcus pneumoniae* or *Haemophilus influenzae* infections, with, surprisingly, *Pseudomonas species* being most common. In our study, bacterial culture of healthy subjects would not have been appropriate since previously well subjects would not have a productive cough. The criteria that we used for bacterial infection, the presence of recognised pathogens in 10⁵ dilution of sputum show that bacteria cause infections more than previously supposed. In unpublished data,³ the detection of pneumococcal antigen in measurable titre in sputum equated well with other evidence of lower respiratory pneumococcal infection, supporting the idea that detection of bacterial antigen is a useful added method.

We feel that viral infection is probably important in the initiation of many bacterial infections of respiratory tract but that the secondary bacterial infection is likely to be a cause of morbidity as well as being potentially amenable to antimicrobial therapy. We too look forward to the day when more sensitive and specific tests are available for investigating this very common clinical problem.

Nottingham City Hospital NHS Trust,
Hucknall Road,
Nottingham NG5 1PR, UK

J. T. MACFARLANE
A. COLVILLE

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SIR,—Community-acquired adult LRTI is common, as Dr Macfarlane and colleagues point out. Sputum and blood cultures have become routine for all patients with fever and chest radiographic changes compatible with pneumonia. 20-30% of blood cultures are claimed to be positive and blood cultures are regarded as essential in all patients suspected of pneumonia.^{1,2} We examined blood cultures from a total of 277 patients admitted with suspected pneumonia to evaluate their value as a diagnostic aid. The spectrum of pathogens proved similar to that recorded in the community by Macfarlane and colleagues. All patients had clinical signs of pneumonia—ie, fever, shortness of breath, and radiological changes on their chest radiograph. 130 patients had 20 mL and 147 had 40 mL venous blood drawn to investigate whether the amount of blood affected the sensitivity of the test. Patients underwent standard treatment and subsequently received penicillin 2 million IU intravenously thrice daily until their clinical condition allowed oral penicillin treatment:

No	mL blood drawn	Positive cultures	Diagnostic sensitivity
130	20	13%	2%
147	40	9%	1%

In the 130 patients with 20 mL samples (10 mL for aerobic and 10 mL for anaerobic culturing) *Streptococcus pneumoniae* was isolated in 6 (2 patients were treated with penicillin before admission), *Staphylococcus epidermidis* in 2 (probably contamination), and *Haemophilus influenzae*, *Escherichia coli*, and *Klebsiella pneumoniae* in 1 each. 45 patients (35%) were treated with antibiotics before admission and blood culture: only 2 patients, 1 with *E coli* (ampicillin) and 1 with *Klebsiella pneumoniae* (penicillin) had their antibiotic treatment changed on the basis of the microbiological diagnosis. In the 147 patients with 40 mL blood samples (20 mL for aerobic and 20 mL for anaerobic culturing), *Streptococcus pneumoniae* (sensitive to penicillin) was isolated in 8 and *Staphylococcus aureus* in 1. This last patient had his antibiotic treatment changed on the basis of the microbiological diagnosis and lack of response to penicillin treatment. 50 patients (34%) received antibiotics before admission and blood culture.

Blood cultures in the diagnosis of microbiological pathogens in radiologically verified pneumonia had a low diagnostic sensitivity of less than 1%—ie, in 277 patients, antibiotic treatment was changed

in only 3 as a result of blood cultures. We therefore suggest that blood cultures are used in cases of severe life-threatening pneumonia only. Diagnostic sensitivity does not seem to be affected by the amount of blood drawn. Penicillin seems still to be first choice in community-acquired, radiological-verified pneumonia.

L. RAVNBORG
F. TØNNESEN
P. EIKEN
A. EIGTVED
L. C. LAURSEN

Pulmonary Department P,
Bispebjerg Hospital,
2400 Copenhagen, Denmark

1. Pneumonia. In: Seaton A, Seaton D, Leitch AG, eds. Crofton and Douglas's Respiratory Diseases. 4th edition. London: Blackwell Scientific Publishers, 1989: 285-345.
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High-dose aspirin, thrombin, and coronary angioplasty

SIR,—During percutaneous transluminal coronary angioplasty (PTCA), maximum inhibition of platelet activation and thrombin generation is required.¹ Recent data suggest that current antiplatelet and anticoagulant regimens fail to achieve this.^{2,3} We have compared the effect of high doses of aspirin with that of conventional aspirin doses on thrombin formation after PTCA.

Plasma concentrations of prothrombin fragment 1 + 2 (F1 + 2), an index of thrombin generation, were measured by enzyme-linked immunosorbent assay (Enzygnost F1 + 2, Behring) 1 hour before and 90 minutes after the end of elective single-vessel PTCA in 24 patients. All patients received 10 000 IU heparin as an intravenous bolus at the start of PTCA, and aspirin 75 mg or 300 mg orally per day for at least 5 days before the procedure. 9 patients received an additional dose of 1000 mg aspirin as an intravenous infusion over the 90 minutes covering the procedure.

In the higher-dose aspirin group (n = 9), mean (SE) F1 + 2 after PTCA was half that in the lower-dose group (n = 15): 0.20 (0.04) versus 0.42 (0.06) nmol/L; F1 + 2 before PTCA was 1.26 (0.16) and 1.24 (0.22), respectively (high versus low dose after PTCA, p < 0.01; before versus after, p < 0.001 in both groups).

Because thrombin is essential for platelet deposition at the site of angioplasty⁴ and can activate smooth-muscle cell growth⁴ and contraction,⁵ maximum suppression of thrombin generation during PTCA may reduce the risk of acute thrombotic complications and the mitogenic and vasospastic stimulation associated with restenosis.⁶ The combination of heparin and high-dose aspirin in patients undergoing PTCA warrants further investigation. The regimen may also prove useful in the treatment of unstable coronary syndromes.

FELICITA ANDREOTTI
GRAHAM J. DAVIES
SHAHROM B. UJANG
PIYAMITR SRITARA

Royal Postgraduate Medical School,
London W12 0NN, UK

Gaubius Laboratory,
IVVO TNO,
Leiden, Netherlands

CORNELIS KLUFT
ATTILIO MASERI

Catholic University,
Rome, Italy

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