alveolar cell traffic, that Porter highlights, may not be readily made in mice. In sharp contrast to humans, mice lack a bronchial circulation. The dominance of the pulmonary circulation is reflected in the work carried out by Corry *et al*. These authors repeatedly emphasise that their studies concern parenchymal leucocytes. When egression is inhibited, leucocytes accumulate in pulmonary parenchymal tissues 'causing' severely impeded gas exchange.[4] Oxygen is an effective remedy in these lethally affected mice.[3] Corry *et al*[3] particularly underscore that 'differences in smooth muscle or other contractile cell function cannot explain the increased mortality observed.' Hence, Porter's statement that death in this model is by 'bronchoconstriction' is puzzling. Then Porter discusses data suggesting that mouse lung injury evoked by intratracheal bleomycin is caused by transepithelial neutrophil egression. We are not equally convinced. For example, n-formyl-neoleucyl-leucyl-phenylalanine (nFNLP) may not be used as a specific inducer of neutrophil egression, as quoted by Porter. nFNLP-like peptides are multipotent agents and avidly induce neutrophil toxicity as well.

Nearly 130 years have passed since Julius Cohnheim held classic lectures on inflammation.[5] He discussed the resolution of inflammatory infiltrates in mucosally lined organs, specifically noting the advantageous outward transport available to bronchi and lung alveoli. Cohnheim's contemporary and perpetual authority, Henry Hyde Salter, observed cell-rich sputum production at resolution of severe asthma. Salter intriguingly analysed how the most peripheral airways could be cleared of cellular exudates since coughing would have little impact here.[6] It seems overdue to fill in the large gaps in our knowledge concerning clearance of cells from the human bronchiolar–alveolar lumen.

Carl G Persson,[1] Lena Uller[2]

[1]Department of Clinical Pharmacology, Laboratory Medicine, Lund University Hospital, Lund, Sweden; [2]Department of Experimental Medical Science, Lund University, Lund, Sweden

Correspondence to Professor Carl G Persson, Department of Clinical Pharmacology, Laboratory Medicine, Lund University Hospital, Lund, Sweden; carl.persson@med.lu.se

Funding From Swedish Medical Research Council.

Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 5 January 2011
Published Online First 20 April 2011

Thorax 2011;**66**:1095–1096.
doi:10.1136/thx.2010.158220

REFERENCES

1. **Porter JC.** Exit of leucocytes across the alveolar epithelium worsens lung injury. *Thorax* 2011;**66**:1095.
2. **Persson CG,** Uller L. Resolution of cell-mediated airways diseases. *Respir Res* 2010;**11**:75.
3. **Persson CG,** Erjefält J, Uller L, *et al*. Unbalanced research. *Trends Pharmacol Sci* 2001;**10**:538–41.
4. **Corry DB,** Rishi K, Kanellis J, *et al*. Decreased allergic lung inflammatory cell egression and increased susceptibility to asphyxiation in MMP2-deficiency. *Nat Immunol* 2002;**3**:347–63.
5. **Cohnheim J.** *Vorlesungen uber allgemeine Pathologie II*. Entzundung 1882.
6. **Salter Henry Hyde**. *On Asthma, its Pathology and Treatment*. 2nd edn. London: Churchill, 1868.

Can cells other than Th17 lymphocytes be important sources of IL-17 in the lungs?

We read with interest the recent paper by Facco *et al* which showed that Th17 cells are present in blood, bronchoalveolar lavage (BAL) and lung tissue from people with sarcoidosis. The authors conclude that Th17 cells are involved in the pathogenesis of sarcoidosis as a multisystem disorder.[1]

Interestingly, the paper mentions expression of interleukin (IL)-17 protein by macrophages. Currently, a strong emphasis exists in the literature on the role of Th17 lymphocytes in the production of IL-17 in the lungs. However, Th17 cells are not the only source of IL-17 identified.[2] IL-17 is also known to be produced by γδ and natural killer T cells.[3 4] It has also been suggested that in human alcoholic liver disease, atherosclerosis and rodent models of lipopolysaccharide-induced airway inflammation IL-17 can be localised to neutrophils.[5–7] Furthermore, we have recently demonstrated that IL-17 protein expression is raised in the lower airway of people with advanced cystic fibrosis lung disease.[8] This IL-17 protein expression was immunolocalised to both neutrophils and mononuclear cells.[8]

It is known that granulocytes may be part of the inflammatory process in sarcoidosis.[9 10] The BAL method used by Facco *et al* was referenced, via the online supplement, to an original paper that used a 200 ml lavage. A differential cell count seems to have been produced from a cytospin, but in the table listing differential BAL data the percentage of neutrophils was not stated.

It would therefore be of interest if the authors could clarify the methodology used for the BAL and differential cell counts, whether any neutrophils were detected in BAL from people with sarcoidosis, and if so, did neutrophils demonstrate IL-17 immunolocalisation? Such data may support a paradigm indicating that IL-17 expression may involve cells in addition to Th17 lymphocytes in sarcoidosis. This may also be relevant to other lung pathologies where IL-17 is implicated.

Malcolm Brodlie,[1,2] James Lordan,[1,3] Christopher Ward[1]

[1]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK; [2]Department of Respiratory Paediatrics, Great North Children's Hospital, Newcastle upon Tyne, UK; [3]Cardiopulmonary Transplantation Unit, Freeman Hospital, Newcastle upon Tyne, UK

Correspondence to Dr Malcolm Brodlie, c/o Paediatric Respiratory Secretaries, Old Children's Outpatients Department, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK; m.j.brodlie@ncl.ac.uk

Funding Medical Research Council, Cystic Fibrosis Trust.

Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 4 January 2011
Published Online First 15 March 2011

Thorax 2011;**66**:1096.
doi:10.1136/thx.2010.157941

REFERENCES

1. **Facco M,** Cabrelle A, Teramo A, *et al*. Sarcoidosis is a Th1/Th17 multisystem disorder. *Thorax* 2011;**66**:144–50.
2. **Cua DJ,** Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. *Nat Rev Immunol* 2010;**10**:479–89.
3. **Michel ML,** Keller AC, Paget C, *et al*. Identification of an IL-17-producing NK1.1(neg) iNKT cell population involved in airway neutrophilia. *J Exp Med* 2007;**204**:995–1001.
4. **Roark CL,** Simonian PL, Fontenot AP, *et al*. Gammadelta T cells: an important source of IL-17. *Curr Opin Immunol* 2008;**20**:353–7.
5. **Lemmers A,** Moreno C, Gustot T, *et al*. The interleukin-17 pathway is involved in human alcoholic liver disease. *Hepatology* 2009;**49**:646–57.
6. **Ferretti S,** Bonneau O, Dubois GR, *et al*. IL-17, produced by lymphocytes and neutrophils, is necessary for lipopolysaccharide-induced airway neutrophilia: IL-15 as a possible trigger. *J Immunol* 2003;**170**:2106–12.
7. **Li L,** Huang L, Vergis AL, *et al*. IL-17 produced by neutrophils regulates IFN-gamma-mediated neutrophil migration in mouse kidney ischemia-reperfusion injury. *J Clin Invest* 2010;**120**:331–42.
8. **Brodlie M,** McKean MC, Johnson GE, *et al*. Raised interleukin-17 is immuno-localised to neutrophils in cystic fibrosis lung disease. *Eur Respir J* 2011;**37**:1378–85.
9. **Lin YH,** Haslam PL, Turner-Warwick M. Chronic pulmonary sarcoidosis: relationship between lung lavage cell counts, chest radiograph, and results of standard lung function tests. *Thorax* 1985;**40**:501–7.
10. **Kelly CA,** Ward C, Stenton SC, *et al*. Assessment of pulmonary macrophage and neutrophil function in sequential bronchoalveolar lavage aspirates in sarcoidosis. *Thorax* 1988;**43**:787–91.

Authors' response

We thank Dr Brodlie and coworkers for their letter[1] and fully agree on the necessity to evaluate whether cells other than lymphocytes and macrophages are involved in IL-17 release in sarcoid lungs. The main manifestation of sarcoidosis is an accumulation of mononuclear inflammatory cells, mostly $CD4^+$ T cells and monocytes/macrophages in involved organs, including the lungs.[2] As specified in our 'Materials and methods' section, we evaluated cells obtained by filtering bronchoalveolar lavage (BAL) fluid through gauze. A standard morphological and immunological analysis of BAL cellular components was performed. The analysis included cell recovery and differential count of macrophages, lymphocytes, neutrophils

Table 1 Bronchoalveolar lavage features of sarcoidosis patients and control subjects

	Cell recovery ($\times10^3$)	Alveolar macrophages ($\times10^3$ (%))	Lymphocytes ($\times10^3$ (%))	Neutrophils ($\times10^3$ (%))
Active sarcoidosis (n=25)	333±73	249±58 (74±6)	82±27 (25±6)	2.5±2.5 (0.8±0.9)
Inactive sarcoidosis (n=11)	109±31	102±27 (94±4)	5±4 (4±2)	0.6±0.9 (0.5±0.8)
Controls (n=10)	128±27	119±27 (93±3)	9±4 (7±4)	0.5±0.8 (0.4±0.7)

and eosinophils (table 1) coupled with a flow cytometry analysis of BAL cells.

Table 1 integrates information given in our published paper,[2] clearly demonstrating that the number of BAL neutrophils was fair in our case series. This unfortunately prevented a definitive evaluation of whether polymorph nucleates represent a source of IL-17. Nonetheless, as shown in figure 1, in selected cases with a significant number of BAL neutrophils (two subjects) a certain degree of IL-17 expression was shown. Experiments are in progress in our lab aimed at evaluating the role of the IL-17 and neutrophil interaction in fibrogenic diffuse parenchymal lung disease (DPLD), including sarcoidosis. In fact, neutrophils are known to play a crucial role in alveolar injury mechanisms in idiopathic pulmonary fibrosis and other types of DPLD. Furthermore, it has recently been shown that Th17 cells and IL-17A favour the development of fibrosis in a murine model of bleomycin-induced pulmonary fibrosis.[3] Finally, patients with idiopathic pulmonary fibrosis show high BAL levels of IL-17.[3]

Concerning putative mechanism through which IL-17 could in theory regulate neutrophil activation and recruitment, we are evaluating whether pulmonary IL-17 favours granulopoiesis in DPLD (via granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor)[4 5] and induces neutrophil chemotaxis through stimulation of endothelial and epithelial cells. Nonetheless, it is important to note that IL-17 also has the capability of mediating neutrophil apoptosis and neutrophil phagocytosis through macrophages.[6] Thus, since IL-17 regulates both recruitment and turnover of neutrophils, we are assessing whether lung IL-17 upmodulates or downmodulates neutrophils during the different phases of DPLD, including sarcoidosis.

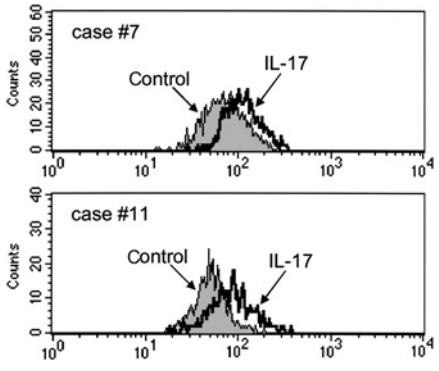

Figure 1 Analysis of IL-17 expression in neutrophils freshly obtained from the bronchoalveolar lavage (BAL) of two sarcoid patients (5% and 4% of BAL cells were neutrophils, respectively). Neutrophils were identified on the basis of CD16 positivity and morphological gating. As shown by the IL-17 staining profile, a faint positivity for the cytokine was detectable in both subjects.

Monica Facco,[1,2] Anna Cabrelle,[1,2] Carlo Agostini[1,2]

[1]Department of Clinical and Experimental Medicine, Hematology-Immunology Section, Padua University School of Medicine, Padova, Italy; [2]Venetian Institute of Molecular Medicine, Padua University School of Medicine, Padova, Italy

Correspondence to Prof Carlo Agostini, Padua University School of Medicine, Giustiniani 2, Padova, 35128, Italy; carlo.agostini@unipd.it

Competing interests None.

Ethics approval This study was conducted with the approval of the Padua Ethics Committee.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 17 January 2011
Published Online First 15 March 2011

Thorax 2011;**66**:1096–1097.
doi:10.1136/thx.2011.159558

REFERENCES

1. **Brodlie M,** Lordan J, Ward C. Can cells other than Th17 lymphocytes be important sources of IL-17 in the lungs? *Thorax* 2011;**66**:1096.
2. **Facco M,** Cabrelle A, Teramo A, *et al*. Sarcoidosis is a Th1/Th17 multisystem disorder. *Thorax* 2011;**66**:144–50.
3. **Wilson MS,** Madala SK, Ramalingam TR, *et al*. Bleomycin and IL-1beta-mediated pulmonary fibrosis is IL-17A dependent. *J Exp Med* 2010;**207**:535.
4. **Schwarzenberger P,** Huang W, Ye P, *et al*. Requirement of endogenous stem cell factor and granulocyte-colony-stimulating factor for IL-17-mediated granulopoiesis. *J Immunol* 2000;**164**:4783.
5. **Laan M,** Prause O, Miyamoto M, *et al*. A role of GM-CSF in the accumulation of neutrophils in the airways caused by IL-17 and TNF-alpha. *Eur Respir J* 2003;**21**:387.
6. **Silverpil E,** Glader P, Hansson M, *et al*. Impact of Interleukin-17 on macrophage phagocytosis of apoptotic neutrophils and particles. *Inflammation* 2011;**34**:1–9.

Intrapulmonary shunting associated with sildenafil treatment in a patient with idiopathic pulmonary arterial hypertension

We reported a case of a 30-year-old Hispanic patient with a history of idiopathic pulmonary arterial hypertension (PAH). A baseline catheterisation showed a mean pulmonary artery pressure (PAP) of 58 mm Hg, capillary wedge pressure of 14 mm Hg, cardiac index of 2.7 l/min/m^2 and pulmonary vascular resistance of 7.5 WU, with no response to adenosine. A pulmonary CT scan ruled out thromboembolism or significant abnormalities (such as glass opacities, septal lines or mediastinal node enlargement commonly seen in venocclusive disease[1]); albumin macroaggregate lung perfusion scan showed normal perfusion without significant intrapulmonary shunt (IPS). He was started on diuretics, oxygen and sildenafil 25 mg three times a day. Despite treatment, dyspnoea worsened and 2 months later the patient was referred to our centre. At admission, the patient was in WHO functional class (FC) IV; his resting PaO_2 had dropped to 56 mm Hg. No decompensating factor was identifiable. A saline-contrast transthoracic echocardiography (SC-TTE) showed a dilated right ventricle (70 mm) with mild ventricular dysfunction and an estimated systolic PAP of 100 mm Hg. Peripheral injection of 10 ml agitated saline evidenced delayed appearance of bubbles in the left atrium, suggestive of IPS (figure 1). After discontinuing sildenafil for 48 h, his PaO_2 improved to 64 mm Hg and the SC-TTE showed no evidence for IPS. Thirty minutes after a challenge dose of 50 mg sildenafil orally, the SC-TTE evidenced IPS recurrence with a PaO_2 drop to 55 mm Hg despite oxygen administration. After permanent discontinuation of sildenafil, the patient had a significant clinical improvement and was discharged with nebulised iloprost 5 μg four times a day. At 6 months follow-up, he remains in FC II without further hospitalisations.

Hypoxaemia in PAH patients might be due to ventilation–perfusion mismatch, depression of cardiac output or right-to-left shunting. SC-TTE offers a fast, non-invasive approach to diagnose right-to-left shunting. Under normal circumstances, saline microbubbles only appear in the right heart chambers. Presence of microbubbles in the left chambers suggests an arteriovenous connection, either due to an atrial septal defect, ventricular septal defect with Eisenmenger's syndrome or IPS. The time frame for contrast appearance in the left chambers allow to differentiate between intracardiac shunting (one or two cardiac cycles after its appearance in right chambers) and IPS (four to eight cycles).[2] Sildenafil administration in PAH patients is associated with a significant reduction of pulmonary-to-systemic vascular resistance ratio, with improvement in arterial oxygenation and 6 min walk distance.[3] However, any vasodilator may theoretically exacerbate hypoxaemia by increasing perfusion to poorly ventilated areas in patients with lung disease, resulting in further ventilation–perfusion mismatch. Kleinsasser *et al*[4] demonstrated, in a porcine model, that a high dose of sildenafil results in a dose-dependent fall in vascular pulmonary resistance associated with a marked increase