1—Nosocomial pneumonia in the intensive care unit: mechanisms and significance

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The true incidence and importance of nosocomial pneumonia in the intensive care unit are difficult to assess. The commonly quoted incidence of 21–26%[1–3] may be an overestimate resulting from the lack of specificity of clinical diagnostic criteria in the critically ill.[4 5] Conventionally, fever, leucocytosis, purulent sputum, and the appearance of new and persistent infiltrates on the chest radiograph are diagnostic of pneumonia.[6 7] Although these criteria are probably satisfactory for patients in general wards, in the intensive care unit such features as fever and leucocytosis may result from various infectious or even non-infectious disease processes. The presence of an endotracheal tube may cause local inflammation and the production of purulent sputum. Radiographic infiltrates consistent with pneumonia may represent other conditions, such as mucus retention, atelectasis, or pulmonary infarction. The diagnosis of nosocomial pneumonia is particularly difficult in patients with widespread infiltrates due to the adult respiratory distress syndrome. Even positive blood cultures cannot be accepted as definitive proof of lung infection as the organisms may arise from a non-pulmonary source.

Microbiological analysis of sputum or tracheal aspirates obtained via the endotracheal tube adds little to diagnostic accuracy and indeed may be misleading. Colonisation of the endotracheal tube and tracheobronchial secretions with potential pathogens occurs within hours of intubation, and distinguishing between tracheobronchial colonisation and pulmonary infection is difficult even if quantitative cultures are used.[2 8] A clinical pulmonary infection score has recently been proposed that combines individually weighted clinical indices and tracheal aspirate results.[9] Its predictive value for the diagnosis of pneumonia approaches that of bronchoscopic criteria.

Only relatively recently have studies of nosocomial pneumonia used techniques for obtaining microbiological specimens that minimise contamination by upper airway secretions.[4 10–16] Quantitative culture of bronchoscopic protected brush specimens, telescoping plugged catheter specimens, and bronchoalveolar lavage fluid has enabled bacteriological criteria to be more accurately defined for the diagnosis of pneumonia in terms of the number of organisms or colony forming units (cfu) per millilitre. Studies in ventilated patients and in the ventilated baboon model indicate that counts of more than 10^3 cfu/ml from protected brush specimens or telescoping plugged catheter specimens[4 10 15 16] and of more than 10^4 or 10^5 cfu/ml from lavage fluid[9 12 17] signify lung infection. The sensitivity and specificity of the techniques using protected brush specimens, telescoping plugged catheter specimens, and lavage fluid range from 70% to 100% (table 1).

The gold standard for the diagnosis of nosocomial pneumonia is probably the histological examination and quantitative culture of lung biopsy specimens. The reliability of the techniques using lavage fluid and protected brush specimens has been shown by culture and histopathological examination of post-mortem lung biopsy material obtained immediately after the bronchoscopic procedures.[10 12]

In the intensive care unit transthoracic, transbronchial or open lung biopsies are generally reserved for immunocompromised patients and for those with suspected interstitial or vasculitic lung disease. In these patients the potential benefit outweighs the morbidity and mortality associated with such invasive procedures.

The use of cultures of bronchoscopy specimens reduces the estimated incidence of pneumonia from 26% to 9%.[14] In Oxford our use of a combination of a weighted clinical criteria score and alternate day bronchiolar lavage via a non-directed suction catheter (non-directed bronchiolar lavage) has yielded an incidence of 11%. We believe that the decision to initiate, withhold, or discontinue antibiotic treatment should be based on these more stringent diagnostic criteria.

Mechanisms

Mechanical ventilation itself has been viewed as the major risk factor for nosocomial pneumonia in the intensive care unit. The endotracheal tube bypasses natural upper airway filters and, like many of the drugs given to the ventilated patient, interferes with laryngeal and cough reflexes and impedes mucociliary clearance. More recent concepts of pathogenesis place greater emphasis on abnormal bacterial colonisation of the respiratory and gastrointestinal tract, aspiration, transmural migration and haematogenous spread of enteric bacteria, and immunoregulation in the critically ill. The evidence supporting these views will be examined.

VENTILATOR ASSOCIATED PNEUMONIA

In the 1960s epidemics of ventilator associated

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Table 1 Specificity and sensitivity of microbiological sampling techniques for the diagnosis of pneumonia in the intensive care unit

Reference	Technique	Threshold (cfu/ml)	Sensitivity (%)	Specificity (%)
Torres[8]	BAL	10^3	56*	71
	TPC	10^3	56*	86
	TA			14
Guerra[17]	BAL	10^4	83	100
Pugin[9]	BAL	BI > 5	93	100
	NBL	BI > 5	73	96
	TA		73	43
Pham[16]	PSB	10^3	65	93
	TPC	10^3	100	82
Oxford	NBL	10^4	74*	81

PSB—protected specimen brush; TPC—telescoping plugged catheter; BAL—bronchoalveolar lavage; NBL—non-directed bronchiolar lavage; TA—tracheal aspirate; BI—bacterial index obtained by logarithmic sum of individual organisms.
*Torres: overall sensitivity 56%, nosocomial 72%, community acquired 22%. Oxford: overall sensitivity 74%, nosocomial 96%, community acquired 31%. Low sensitivity for diagnosis of community acquired pneumonia attributed to prior antibiotic treatment.

pneumonia were caused by bacterial contamination of ventilators, nebulisers, humidifiers, or tubing. Improvements in ventilator design and the implementation of rigorous infection control measures have largely prevented these epidemics, and now most cases of pneumonia in the intensive care unit follow infection with endogenous organisms.

Changing the ventilator circuit daily was intended to reduce the risk of developing a reservoir of pathogens, but renewing circuits every 48 hours rather than 24 hours makes no difference to the level of colonisation of the circuits, and was actually found to reduce the incidence of pneumonia.[1] The adverse effect of more regular circuit changes has been attributed to spillage of heavily contaminated condensate into the tracheobronchial tree during manipulation of the tubing. A recent prospective study of circuit changes every 48 hours compared with no change throughout the period of ventilation indicated no difference in the degree of colonisation of circuits or patients (assessed by pharyngeal swabs and tracheal aspirates), and no increase in the incidence of pneumonia diagnosed from protected brush specimens.[18] In most cases ventilator circuits are contaminated by the patient rather than the reverse.

None the less, several studies have indicated that endotracheal intubation is a major factor contributing to the reported high rate of nosocomial pneumonia in the intensive care unit. Patients who are intubated and ventilated have been shown to have a seven fold increase in the incidence of clinically diagnosed pneumonia.[19] The risk seems to increase with the duration of ventilation and, if pneumonia is diagnosed by clinical criteria alone, appears maximal in the first 10 days in hospital, few cases being identified thereafter.[20] In contrast, when criteria for establishing the diagnosis of pneumonia are based on the use of protected brush specimens, the risk appears constant over the whole period of ventilation.[14]

Table 2 Bacteria causing pneumonia in the critically ill

	Fagon et al[14]	Torres et al[8]	Oxford
No of episodes pneumonia	52	25	36
Technique	PSB	TPC + BAL	NBL
Threshold count (cfu/ml)	10^3	10^3	10^4
GRAM NEGATIVE BACTERIA	*No (%)**	*No (%)**	*No (%)**
Pseudomonas aeruginosa	16 (31)	7 (28)	6 (16)
Acinetobacter spp	8 (15)	6 (24)	0
Proteus spp	8 (15)	0	0
Moraxella catarrhalis	5 (10)	0	1 (3)
Haemophilus spp	5 (10)	0	4 (11)
Escherichia coli	4 (8)	3 (12)	1 (3)
Klebsiella spp	2 (4)	3 (12)	0
Enterobacter cloacae	1 (2)	1 (4)	4 (11)
Pseudomonas maltophila	0	0	2 (5)
Legionella spp	1 (2)	2 (10)	0
Miscellaneous	1 (2)	1 (4)	1 (3)
GRAM POSITIVE BACTERIA			
Staphylococcus aureus	17 (33)	5 (20)	2 (5)
Streptococcus pneumoniae	3 (6)	1 (4)	2 (5)
Other streptococci	8 (15)	4 (16)	2 (5)
Corynebacteria spp	4 (8)	0	0
Staphylococcus epidermidis	0	1 (4)	0
ANAEROBES	1 (2)	1 (4)	0
POLYMICROBIAL FLORA	21 (40)	10 (40)	7 (19)

*Sum of percentages exceeds 100% owing to polymicrobial flora.
Abbreviations as in table 1.

MICROBIOLOGICAL CHARACTERISATION

From bronchoscopic studies[8 14] and from our own investigations using bronchiolar lavage, a characteristic range of organisms have been identified in the lungs of patients with pneumonia in the intensive care unit (table 2). Although Gram positive organisms and *Haemophilus influenzae* are common in community acquired pneumonia,[9 14] Gram negative aerobic bacteria predominate in nosocomial pneumonia (pneumonia developing after 48 hours in hospital or intensive care unit).

Some studies of intensive care patients have emphasised the high incidence of apparently polymicrobial infections occurring in 50–87% of cases of pneumonia.[9 12] In these studies pneumonia was defined on the basis of a bacterial index calculated from the log sum of the colony counts for the individual organisms. This calculation includes organisms grown at very low concentrations that would in other studies be considered colonising agents or contaminants. Stipulation of a threshold of over 10^4 cfu/ml in lavage fluid for any individual organism,[17] or bacteraemia,[21] yields the much lower incidences of polymicrobial pneumonia of 26% and 12% respectively. Our experience in Oxford with the non-directed bronchiolar lavage technique and a threshold of 10^4 cfu/ml indicates a 19% incidence of polymicrobial pneumonia. The choice of sampling technique (protected brush specimens, bronchoalveolar lavage, or non-directed bronchiolar lavage), volume of lavage fluid instilled, and the threshold colony counts used in the definition of pneumonia will clearly all influence the reported incidence.

In this review, we have focused on the broadly immunocompetent patient. Pneumonia in the immunocompromised patient in the intensive care unit may be due to organisms as diverse as cytomegalovirus, *Pneumocystis carinii*, *Mycobacterium avium-intracellulare*, and fungi. The principals of diagnosis remain the same but the threshold for initiating antibiotic treatment may be lower.

COLONISATION OF THE RESPIRATORY TRACT IN VENTILATED PATIENTS

Upper airway colonisation

The changing range of organisms causing pneumonia in the intensive care unit is paralleled by changes in colonisation of the oropharynx and the gastrointestinal tract (table 3). In normal healthy subjects the nasal passages and oropharynx are colonised by Gram positive, mainly anaerobic, commensals, whereas the trachea and distal airways are sterile, or yield counts below 10^4 cfu/ml.[22] Johanson[23] was the first of several authors[24–26] to show that in hospital the oropharynx becomes colonised by Gram negative aerobic bacteria and to propose that aspiration of these organisms, with reduced mucociliary clearance, leads to nosocomial pneumonia.[23] The incidence of abnormal colonisation paralleled the severity of underlying illness, increasing from 35% in the moderately ill to 73% in the severely ill.[23] In the intensive care unit abnormal colonisation (table 4) has been shown to increase with duration of stay,[27–29] and to have been present in most patients who subsequently develop pneumonia.[6]

Bacterial adherence

The earliest stage of bacterial colonisation is bacterial adherence to the epithelium of the respiratory tract, which is promoted by severe illness, malnutrition, intubation, tracheostomy, uraemia, cigarette smoking, and ciliary dysfunction.[30] In healthy people bacteria are prevented from adhering to epithelial surfaces, such as the oropharynx, by fibronectin and IgA. Fibronectin is a cell surface glycoprotein, which has binding sites for Gram positive bacteria but at the same time prevents the adherence of *Pseudomonas* spp and Enterobacteriaceae. In critically ill patients the protective fibronectin layer is destroyed by proteases present in saliva[31] or released from neutrophils,[32] so that epithelial cell surface receptors are exposed; these are then available for bacterial adherence. Similarly, proteases may break down IgA, so impairing this mechanism of blocking bacterial adherence.[32]

Table 3 Colonising organisms of the oropharynx and upper gastrointestinal (GI) tract[23 44]

Normal commensals of the oropharynx ($10^8 - 10^{10}$ cfu/ml)	*Abnormal commensals of the oropharynx and upper GI tract ($10^3 - 10^8$ cfu/ml)*
AEROBES	
α-Haemolytic streptococci	*Klebsiella*
Streptococcus pneumoniae	*Enterobacter*
Staphylococcus spp	*Acinetobacter*
Neisseria spp	*Pseudomonas*
Haemophilus influenzae	*Serratia*
Moraxella catarrhalis	*Proteus*
Escherichi coli	*Morganella*
Candida	*Citrobacter*
ANAEROBES	
Peptostreptococcus	
Fusobacterium	
Bacteroides	
Veilonella	
ACID RESISTANT ORAL BACTERIA SURVIVING IN THE STOMACH AND UPPER SMALL INTESTINE ($<10^3$ cfu/ml)	
Streptococcus spp	
Staphylococcus spp	
Lactobacillus	
Candida	

Table 4 Risk factors associated with oropharyngeal colonisation[30]

Severity of illness*
Prolonged hospitalisation
Prolonged stay in intensive care unit
Advanced age
Antibiotic therapy
Endotracheal intubation*
Tracheostomy*
Gastric acid suppressing therapy
Major surgery*
Malnutrition
Smoking*
Pre-existing lung disease
Uraemia*

*Risk factor shown to increase bacterial adherence.

Most Gram negative aerobic bacteria colonise the oropharynx before reaching the lower respiratory tract, but *Pseudomonas* spp has been shown to colonise the trachea without prior colonisation of the oropharynx.[33] This tropism may be due to the preferred adherence of *Pseudomonas* to ciliated rather than squamous cells.[34] Mechanical injury of the trachea, which might be caused by an endotracheal intubation, has also been shown to promote attachment and growth of *P aeruginosa*.[35]

Lower airway colonisation

Although tracheal colonisation has been studied in mechanically ventilated patients, little is known about the prevalence or pathogenesis of colonisation of the distal airways.[30] We have used alternate day non-directed bronchiolar lavage to assess lower airway colonisation in ventilated patients in our general adult intensive care unit. With this technique a sterile suction catheter is introduced into the bronchial tree via the endotracheal tube. The catheter is advanced until substantial resistance is encountered about 40–50 cm from the proximal end of the endotracheal tube. Twenty millilitres of sterile saline are instilled, immediately reaspirated, and sent for quantitative culture. Simultaneous chest radiography has shown that the catheter enters the lower lobe bronchi of, in most cases, the right lung. Surveillance with this simplified lavage technique indicates that in most ventilated patients, as in healthy people, the lower airways remain sterile or yield transient scanty growths of less than 10^4 cfu/ml of Gram positive or Gram negative bacteria, which may represent contamination of the lavage catheter. Quantitative culture of lavage fluid enables differentiation of contamination from colonisation or infection,[22] and we have defined colonisation as a growth of more than 10^4 cfu/ml obtained on more than one occasion in the absence of clinical evidence of lung infection.

Applying these criteria, we found that in eight of 14 patients staying more than 14 days in the intensive care unit there was colonisation of the distal airways with *Pseudomonas* spp or *Acinetobacter*. All these patients were receiving, or had recently completed, a course of antibiotics and had severe underlying

disease, factors that also predispose to *Pseudomonas* and *Acinetobacter* pneumonia.[14] Prolonged colonisation for 7–21 days with *Acinetobacter* or *Pseudomonas maltophila* (recently renamed *Xanthomonas maltophila*) was seen on four occasions, with subsequent clinical evidence of pneumonia requiring antibiotic treatment in only one case. Colonisation with *Pseudomonas aeruginosa* was followed more rapidly (after 2–12 days) by manifestations of clinical infection in all of the remaining six cases. In those six cases antibiotics produced clinical improvement, despite rapid recolonisation with antibiotic resistant variants in two patients. The more rapid decline in patients colonised with *Pseudomonas aeruginosa* accords with the current view of the pathogenicity of this organism.

Transition from colonisation to infection

Transition from colonisation to infection is not well understood. How a stable state of colonisation might progress to infection through the production of inflammatory mediators has been discussed in detail elsewhere.[30 36] It has also been suggested that colonisation of the upper or lower respiratory tract is a marker of a severely ill patient, in whom the multiple defects of host defence that lead to colonisation also allow the progression to invasive infection.[30]

COLONISATION OF THE GASTROINTESTINAL TRACT

In addition to the upper airways, another reservoir of potentially pathogenic bacteria is the gastrointestinal tract. Within 24–72 hours of admission to the intensive care unit Gram negative aerobic bacteria colonise the stomach and small bowel, and compete with anaerobic commensals of the large intestine.[29] Antibiotic resistance is common, possibly as a result of exposure to small quantities of parenteral antibiotics, which reach the gut in saliva, bile and mucus.[37]

Upper airway colonisation may in many cases be due to retrograde flow of gastric secretions, a common occurrence in the intensive care unit because of patients' supine posture, frequent gastroparesis, and the presence of a nasogastric tube, which impairs gastro-oesophageal sphincter function. Furthermore, microaspiration of oropharyngeal and gastric secretions into the trachea is known to occur frequently and is not prevented by the endotracheal tube cuff.[38 39] Radioactively labelled material introduced into the stomach via a nasogastric tube is subsequently found in the oropharynx in 70% of patients and in the lungs in 40% of patients.[40] As aspiration frequently occurs in healthy individuals without infective sequelae, the development of pneumonia in the critically ill may depend on the dose of inoculum, bacterial virulence, and the host's immune response.

As an alternative to aspiration, there is currently much interest in possible translocation of enteric organisms across damaged intestinal mucosa as a mechanism for the development of pneumonia. Both processes may be promoted by several aspects of management in the intensive care unit such as prophylaxis of stress ulcers and loss of enteral feeding.

Gastric luminal pH and stress ulcer prophylaxis

The incidence of massive gastrointestinal bleeding in the intensive care unit has declined over the last 20 years, probably owing to improvement in such general measures as cardiovascular resuscitation, nutrition, and sedation, which affect acid secretion and integrity of the gut mucosa. Stress ulcer prophylaxis with antacids, H_2 antagonists, or cytoprotective agents has become routine, but the contribution of these to the observed reduction in gastrointestinal haemorrhage is in question.[41 42] Furthermore, there is concern that raising gastric pH above 4 antagonises an important natural defence mechanism suppressing bacterial growth in the stomach and upper small intestine.[43]

Colonisation of the stomach by Gram negative aerobic bacteria is promoted by antacids and H_2 antagonists.[27 44 45] A similar increase in the degree of colonisation of the oropharynx and tracheal secretions is seen in ventilated patients receiving gastric acid suppressing treatment.[44] In most cases, however, gastric Gram negative bacillary colonisation follows colonisation of the oropharynx or trachea, so the true importance of retrograde carriage is still disputed.[45–47]

Although alkalinisation of gastric juice promotes abnormal gastric colonisation, and possibly abnormal upper airway colonisation, it is not clear whether it also increases the incidence of nosocomial pneumonia. For example, in a retrospective study of 233 mechanically ventilated patients treatment with H_2 antagonists was associated with an increased incidence of pneumonia.[1] In contrast, in a prospective study of 40 mechanically ventilated neurosurgical patients randomised to receive ranitidine or no stress ulcer prophylaxis there was no significant difference in the rates of pneumonia.[47]

Sucralfate, a mucosal protective agent that does not affect gastric pH, was associated with an 80% lower incidence of pneumonia than antacid treatment.[48] It was not clear from this study, however, whether the two treatment groups were comparable in terms of underlying disease, nutritional regimen, and antibiotic policy. In the widely quoted randomised prospective study by Driks, in which the comparability of the treatment groups was made clear, the incidence of pneumonia among 130 mechanically ventilated patients was 49% in those receiving antacids combined with H_2 antagonists, compared with a 23% incidence in patients having sucralfate. Surprisingly, patients receiving an H_2 antagonist alone had a still lower incidence of pneumonia of 6%.[44]

These studies failed to prove that either antacids or H_2 antagonists alone increase the incidence of pneumonia, perhaps because a single agent applied in conventional doses does not invariably achieve alkalinisation. The combination of two acid suppressing agents may be

more effective in this respect and hence increase the incidence of pneumonia. The apparent beneficial effect of sucralfate on pneumonia and mortality rates may be due in part to its intrinsic bactericidal action.[41 48] Sucralfate also influences the production of prostaglandin (PGE_2), mucus secretion, and mucosal blood flow, and so could promote the integrity of the whole gut mucosa.[41] There is also experimental evidence that sucralfate can reduce bacterial translocation across the intact gut wall,[49] which may play a part in the pathogenesis of nosocomial pneumonia. In cases where stress ulcer prophylaxis is thought to be necessary the balance of evidence, and theoretical considerations, probably favour sucralfate rather than H_2 blockers or antacids.

Many patients in the intensive care unit who are not receiving stress ulcer prophylaxis have a raised gastric luminal pH.[44] This may be related to the inhibitory effect of hypoxia or splanchnic hypoperfusion on the energy requiring process of acid secretion. The incidence of a spontaneously high gastric pH (>4) in mechanically ventilated patients ranges from 52%[44] to 77%.[50] Gastric colonisation persisted in 55% of patients treated with sucralfate after cardiac surgery.[50] As the bactericidal action of sucralfate is pH dependent[48] this may limit the effectiveness of sucralfate as a method of gastric sterilisation.

Selective decontamination of the digestive tract

An alternative method by which the enteric reservoir of pathogens may be reduced is selective decontamination of the digestive tract (SDD). The objective of this is to prevent nosocomial infections, particularly pneumonia. SDD requires the administration of topical non-absorbable antimicrobials to the mouth (as a paste) and stomach (via a nasogastric tube). A typical regimen combines polymixin E, tobramycin or gentamicin, and amphotericin B. These agents preserve normal anaerobic gastrointestinal flora while Gram negative aerobic bacteria and yeasts are eradicated. Several studies have also used parenteral cefotaxime during the first four to seven days in the intensive care unit, to treat subclinical or overt infection with "community" organisms, and to reduce the acquisition of oropharyngeal Gram negative aerobic bacteria during the interval before selective decontamination of the digestive tract is fully established.

Most SDD regimens achieve eradication of oropharyngeal and gastric pathogens after three to four days. Reducing carriage in the rest of the colon is a slower process, dependent on peristaltic activity. In patients with an ileus abolition of rectal carriage can take up to 15 days.[29]

Although the effectiveness of SDD in eradicating oropharyngeal and gastric colonisation appears undisputed, its impact on the incidence of infections, nosocomial pneumonia, and mortality is more controversial. In 21 out of 22 published studies a significant reduction in infection rates was reported, with the greatest impact on Gram negative respiratory tract infections.[51 52]

It may be argued that the inclusion of tracheal aspirate culture as a criterion for infection may lead to overdiagnosis of pneumonia in the control group and underdiagnosis in the group of treated patients, from whom such cultures may yield negative results owing to contamination with the agents used in SDD. In those studies in which the diagnosis of pneumonia was made on clinical grounds alone, however, a significant reduction in pneumonia rate was also seen.[29 53] Furthermore, in two studies using protected sampling techniques positive cultures occurred only in the control groups.[54 55] A more recent study, however, has shown the presence of tobramycin and amphotericin B in lung lavage fluid, though at concentrations less than the mean inhibitory concentration (MIC) of bacteria cultured from simultaneous tracheal aspirates.[56] Whether undiluted distal bronchial secretions contain high enough concentrations of the agents used in SDD to inhibit their growth in vitro is still not clear. Indeed, in some cases aspiration of these agents might directly inhibit lung colonisation or pneumonia.

In contrast to the significant and consistent improvements in infection rates, only two studies have shown a significant reduction in overall mortality.[51] Two further studies reported a reduction in mortality attributable to infections,[53 57] whereas one large study found a reduction in mortality only in the subgroup of patients with trauma.[29] The general lack of impact on mortality may in some trials be due to the relatively small numbers of patients, lack of prognostic stratification, or use of neurosurgical and cardiac patients with low background infection rates, who are thus unlikely to benefit. Meta-analysis of 11 studies (1489 patients) has, however, failed to confirm a reduction in mortality,[58] which may indicate that nosocomial pneumonia is responsible for fewer deaths in the intensive care unit than has previously been assumed.

Resistance to the agents used in selective decontamination of the digestive tract has emerged among some isolates, but as yet no infections with these resistant organisms have followed.[51] This leaves little room for complacency as it may be only a matter of time before infections with organisms resistant to selective decontamination of the digestive tract are seen.

Gut mucosal integrity: its relevance to nosocomial pneumonia

It has been suggested that nosocomial pneumonia might be caused not by aspiration but by bacteria derived from the gut that have migrated from the intestinal lumen to blood across a damaged gut barrier, a process termed gut bacterial translocation.[59 60] This hypothesis is consistent with the results of work relating the incidence of pneumonia to colonisation of the upper gastrointestinal tract as gastric colonisation may promote colonisation of the more distal intestinal tract.[61] Indirect evidence that translocation may cause lung infection comes from human studies using the relatively new technique of gastric or sigmoid tonometry

for monitoring gut mucosal ischaemia. An association has been found between duration and degree of sigmoid ischaemia during surgery and risk of nosocomial pneumonia two to eight days after operation.[61] In addition, in ventilated patients in the intensive care unit nosocomial pneumonia developed exclusively in those patients with gut mucosal injury as determined by gastric tonometry, guiac positive nasogastric aspiration, endoscopic evidence of mucosal injury, or bleeding.[60]

Gut ischaemia and other factors summarised in table 5 have been shown to promote translocation of viable microorganisms across an anatomically intact intestinal barrier. In these mainly experimental studies translocation was measured by recovery of viable organisms from regional lymph nodes, or directly visualised with light and transmission electron microscopy. Sequestration of enteric organisms in mesenteric lymph nodes is also, however, observed in patients with inflammatory bowel disease and, to a lesser extent, in healthy people.[62] Thus the clinical relevance of microbial translocation has yet to be fully established.[63]

Interestingly, in a rat model dissemination of live ^{14}C labelled *Escherichia coli* has been shown to follow translocation provoked by bowel manipulation at laparotomy or ligation of the superior mesenteric artery. Concentrations of live bacteria were highest in the lung followed (in descending order) by the liver, kidney, heart, and spleen.[64] A prospective clinical study, however, in 20 trauma patients at risk of gut ischaemia, using intraoperative portal vein cannulation and sequential blood sampling, has not confirmed significant portal or systemic bacteraemia or gut derived endotoxaemia within the first five days after injury.[65] To prove the importance of bacterial translocation in the critically ill it will ultimately be necessary to show that organisms not only pass through the intestinal wall but consistently enter the portal circulation and survive passage through the liver before lodging in and infecting the lung.

Enteral versus parenteral nutrition

Long held convictions about the value of postoperative total parenteral nutrition are being challenged.[66] In most studies it has not improved outcome. There is evidence of an intravenous lipid related immunosuppressive effect[66] and an increase in infective complications, particularly pneumonia.[59] Moreover, it is now recognised that gut mucosa derives much of its nutrition from the gut lumen. The gut requires short chain fatty acids, produced by anaerobic flora metabolising dietary fibre, and the amino acid glutamine,[67] which is too unstable for inclusion in standard total parenteral nutrition solutions. Animal models confirm that total parenteral nutrition leads to atrophy of the gut mucosa[68] and increased bacterial translocation,[69] whereas enteral nutrition can enhance splanchnic blood flow[70] and, if it contains glutamine, maintain mucosal integrity and reduce bacterial translocation.[67] Glutamine supplementation of total parenteral nutrition may be as beneficial.[67]

In contrast, human studies have shown intact duodenal mucosal morphology[71] and secretion of gut hormones[72] even after 21 days of glutamine deficient total parenteral nutrition. Possibly there is an interspecies variation in mucosal resistance resulting from differences in enterocyte turnover rate (J Macfie, personal communication).

Enteral feeding may not be without adverse effects. One study reported the high incidence of nosocomial pneumonia of 54% in mechanically ventilated patients receiving continuous enteral nutrition.[73] This may be related to neutralisation of gastric acid, for a substantial rise in the number of Gram negative bacteria has been found in gastric juice after the start of enteral feeding.[46] Contamination of enteral feeding solutions at the time of preparation or administration has also led to infection,[74] though the risk with commercially prepared solutions is very low.

Recent recommendations for enteral feeding have included intermittent nasogastric feeding regimens, to allow a period of "natural" sterilisation.[75] In postoperative ileus, which affects primarily the stomach and colon, feeding via nasoduodenal or nasojejunal tubes facilitates the establishment of enteral feeding. Placement of feeding tubes in the duodenum or jejunum may require endoscopic or fluoroscopic guidance but the potential benefits are considerable.

Table 5 Factors promoting translocation of microorganisms as measured by recovery of viable organisms from the regional lymph nodes[50 64 82]

Promoted by
Haemorrhagic shock
Intestinal obstruction
Parenterally administered endotoxin
Hyperpyrexia
Thermal injury
Parenteral feeding
Elemental diets
Cytotoxic drugs
Obstructive jaundice
Antibiotics causing Gram negative bacterial overgrowth
Decreased by
Complete enteral diets
Glutamine
Bombesin
Prevention of intestinal ischaemia
Sucralfate

Importance of nosocomial pneumonia in the intensive care unit

Mortality from nosocomial pneumonia is widely reported to exceed 40% and is assumed to reflect the direct effect of lung infection. There is evidence, however, to suggest that the mortality may be more a function of the severity of the underlying disease than lung infection per se. In one large study, using multivariate analysis, of the risk factors associated with fatality in ventilated patients in the intensive care unit several factors, but not nosocomial pneumonia, were significantly correlated with mortality.[1] In another investigation, a matched cohort study of hospital acquired pneumonia, the excess number of

deaths attributable to pneumonia was only marginally significant.[76] A more recent study, of pneumonia diagnosed by telescoping plugged catheter specimens in mechanically ventilated patients,[77] found the mortality rate of 42% similar to that in ventilated patients without pneumonia (38%).

Indirect support for the idea that most patients in the intensive care unit die with rather than from their nosocomial pneumonia comes from trials of selective digestive tract decontamination, which have had little impact on mortality despite the reduction in the rates of pneumonia and other infections.

The assumption that nosocomial pneumonia is an important cause of morbidity in the intensive care unit is called into question by the findings of three trials of selective decontamination of the digestive tract that preventing pneumonia had no significant effect on duration of time on a ventilator and in the intensive care unit.[53 54 57] By contrast, other studies have shown that nosocomial pneumonia lengthened the mean stay in the intensive care unit by up to 21 days.[77 78]

NOSOCOMIAL PNEUMONIA, SEPSIS SYNDROME, AND MULTIPLE ORGAN FAILURE

Nosocomial pneumonia may be complicated by the sepsis and multiple organ failure syndromes, both of which have a poor prognosis. In the critically ill, however, the chain of causation is often obscure. Clearly in some patients in the intensive care unit pneumonia is the primary event that leads to the sepsis syndrome and multiple organ failure. On the other hand, lung infection may be a consequence of bacteraemia following breakdown of the gut barrier and translocation of bacteria and endotoxin. In these circumstances gut failure initiates the systemic inflammatory response and so provides the "motor of multiorgan failure."[61 65 79 80]

Future considerations

The accurate diagnosis of nosocomial pneumonia rests on the identification of several clinical criteria combined with reliable microbiological tests, as provided by protected brush specimens, telescoping plugged catheter specimens, or lung lavage. Reducing the incidence of nosocomial pneumonia requires a multi-pronged approach. A low gastric pH should be encouraged by avoidance of acid suppressing drugs. Adequate mucosal oxygenation for acid generation must be maintained. The adoption of intermittent rather than continuous nasogastric feeding regimens may be desirable. Nasojejunal feeding offers substantial advantages and reduces the need for total parenteral nutrition. Reservations about the routine use of selective decontamination of the digestive tract in preventing nosocomial pneumonia must remain. Its selective use in patients with, or at risk from, intestinal hypoperfusion or luminal Gram negative colonisation may be justified. There may be a place for other new therapeutic developments, such as prevention of bacterial adherence by topical treatment with protease inhibitors, IgA, or fibronectin,[75] and immunomodulation with monoclonal biopharmaceutical products.[81–83] An integrated approach of this sort might produce a greater impact on mortality as it takes into account the possible interdependence of nosocomial pneumonia, gut barrier function, the sepsis syndrome, and multi-organ failure.

The arguments presented in this review attempt to characterise the importance of nosocomial pneumonia in terms both of its true incidence and direct morbidity and of the attributable mortality. We maintain that nosocomial pneumonia should be viewed not only as a cause but also as a consequence of critical illness. As Louis Pasteur concluded in 1895, "The germ is nothing, the soil is everything."[84]

1 Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. *Am Rev Respir Dis* 1986;**133**:792–6.

2 Salata RA, Lederman MM, Shlaes DM, *et al.* Diagnosis of nosocomial pneumonia in intubated, intensive care unit patients. *Am Rev Respir Dis* 1987;**135**:426–32.

3 Torres A, Aznar R, Gatell JM, *et al.* Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis* 1990;**142**: 523–8.

4 Chastre J, Fagon JY, Soler P, *et al.* Diagnosis of nosocomial bacterial pneumonia in intubated patients undergoing ventilation: comparison of the usefulness of bronchoalveolar lavage and the protected specimen brush. *Am J Med* 1988;**85**:499–506 [see also erratum, *Am J Med* 1989; **86**:258].

5 Garrard CS, Crook DWM. Nosocomial pneumonia in the critically ill. Current Anaesthesia and critical care 1991; 2:155–60.

6 Johanson WG, Peirce AK, Sanford JP, *et al.* Nosocomial respiratory infections with gram-negative bacilli: the significance of colonisation of the respiratory tract. *Ann Intern Med* 1972;77:701–6.

7 Centers for Disease Control. CDC definitions for nosocomial infections. *Am Rev Respir Dis* 1988;**139**:1058–9.

8 Torres A, De La Bellacasa JP, Xaubet A, *et al.* Diagnostic value of quantitative cultures of bronchoalveolar lavage and telescoping plugged catheters in mechanically ventilated patients with bacterial pneumonia. *Am Rev Respir Dis* 1989;**140**:306–10.

9 Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator associated pneumonia by bacteriologic analysis of bronchoscopic and non bronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis* 1991;**143**:1121–9.

10 Chastre J, Viau F, Brun P, *et al.* Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. *Am Rev Respir Dis* 1984;**130**:924–9.

11 Torres A, De La Bellacasa JP, Rodriguez-Roisin R, De Anta MTJ, Agusti Vidal A. Diagnostic value of telescoping plugged catheters in mechanically ventilated patients with bacterial pneumonia using the Metras catheter. *Am Rev Respir Dis* 1988;**138**:117–20.

12 Johanson WJ, Seidenfeld JJ, Gomez P de los Santos R, Coalson JJ. Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. *Am Rev Respir Dis* 1988;**137**:259–64.

13 Fagon JY, Chastre J, Hance AJ, *et al.* Detection of nosocomial lung infection in ventilated patients. Use of a protected specimen brush and quantitative culture techniques in 147 patients. *Am Rev Respir Dis* 1988;**138**:110–6.

14 Fagon JY, Chastre J, Domart Y, *et al.* Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. *Am Rev Respir Dis* 1989;**139**:877–84.

15 Chastre J, Fagon JY, Soler P, *et al.* Quantification of BAL cells containing intracellular bacteria rapidly identifies ventilated patients with nosocomial pneumonia. *Chest* 1989;**95**:190–2S.

16 Pham LH, Brun BC, Legrand P, *et al.* Diagnosis of nosocomial pneumonia in mechanically ventilated patients. Comparison of a plugged telescoping catheter with the protected specimen brush. *Am Rev Respir Dis*

1991;143:1055–61.
17 Guerra L, Baughman RP. Use of bronchoalveolar lavage to diagnose bacterial pneumonia in mechanically ventilated patients. *Crit Care Med* 1990;18:169–73.
18 Dreyfuss D, Djedaini K, Weber P, *et al.* Prospective study of nosocomial pneumonia and of patient and circuit colonisation during mechanical ventilation with circuit changes every 48 hours versus no change. *Am Rev Respir Dis* 1991;143:738–43.
19 Celis R, Torres A, Gatell JM, Almela M, Rodriguez RR, Agusti VA. Nosocomial pneumonia. A multivariate analysis of risk and prognosis. *Chest* 1988;93:318–24.
20 Langer M, Mosconi P, Cigada M, Mandelli M. The Intensive Care Unit Group of infection control: Long-term respiratory support and risk of pneumonia in critically ill patients. *Am Rev Respir Dis* 1989;140:302–5.
21 Bryan CS, Reynolds KL. Bacteremic nosocomial pneumonia. Analysis of 172 episodes from a single metropolitan area. *Am Rev Respir Dis* 1984;129:668–71.
22 Kirkpatrick MB, Bass JB. Quantitative bacterial cultures of bronchiolar lavage fluids and protected brush catheter specimens from normal subjects. *Am Rev Respir Dis* 1989; 139:546–8.
23 Johanson WG, Pierce AK, Sanford JP. Changing pharyngeal bacterial flora of hospitalized patients. *N Engl J Med* 1969;21:1137–40.
24 Higuchi JH, Chaudhui T, Johanson WG. Determinants of postoperative respiratory tract colonisation with Gram-negative bacilli. *Am Rev Respir Dis* 1978;117 (abstracts):274.
25 Valenti WM, Trudell RG, Bentley DW. Factors predisposing to oropharyngeal colonisation in the aged. *N Engl J Med* 1978;298:1108–11.
26 LeFrock JL, Ellis CA, Weinstein L. The relation between aerobic fecal and oropharyngeal flora in hospitalized patients. *Am J Med Sci* 1979;277:275–80.
27 Du Moulin GC, Paterson DG, Hedley-White J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: A frequent cause of post-operative colonisation of the airway. *Lancet* 1982;i:242–5.
28 Stoutenbeek CP, van Saene HFK, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. *Int Care Med* 1984;10:106–13.
29 Ledingham IMA, Alcock SR, Eastaway AT, McKay IC, McDonald JC, Ramsay G. Triple regime of selective decontamination of the digestive tract, systemic cefotaxime, and microbiological surveillance for prevention of acquired infection in intensive care. *Lancet* 1988;i:785–90.
30 Niederman MS, Craven MD, Fein AM, Schultz DE. Pneumonia in the critically ill hospitalized patient. *Chest* 1990;1:170–81.
31 Woods DE, Straus DC, Johanson WG, Bass JA. Role of salivary protease activity in adherence of Gram negative bacilli to mammalian buccal epithelial cells in vivo. *J Clin Invest* 1981;68:1435–40.
32 Niederman MS, Merrill WW, Polomski L, Reynolds HY, Gee GBI. Influence of sputum IgA and elastase on tracheal cell bacterial adherence. *Am Rev Respir Dis* 1986;133: 255–60.
33 Niederman MS, Mantovani R, Schoch P, Pappas J, Fein AM. Patterns and routes of tracheobronchial colonisation in mechanically ventilated patients. The role of nutritional status in colonisation of the lower airway by *Pseudomonas* species. *Chest* 1989;95:155–61.
34 Niedermann MS, Rafferty TE, Sasaki CT, Merrill WW, Matthay RA, Reynolds HY. Comparison of bacterial adherence to ciliated and squamous epithelial cells obtained from the human respiratory tract. *Am Rev Respir Dis* 1983;127:85–90.
35 Yamaguchi T, Yamada H. Role of mechanical injury on airway surface in the pathogenesis of *Pseudomonas aeruginosa*. *Am Rev Respir Dis* 1991;144:1147–52.
36 Geddes DM. Infection *v.* colonisation. *Int Care Med* 1990; 16:201–5.
37 van Saene HKF, Stoutenbeek CP, Miranda DR, Zandstra DF. A novel approach to infection control in the intensive care unit. *Acta Anaesth Belg* 1983;34:193–208.
38 Spray SB, Zuidema GD, Cameron JL. Aspiration pneumonia incidence of aspiration with endotracheal tube. *Am J Surg* 1976;131:701–8.
39 Seegobin RD, Hasselt GL. Aspiration beyond endotracheal cuffs. *Can Anaesth Soc J* 1986;33:273.
40 Ibanez J, Penafiel A, Raurich J, *et al.* Gastrooesophageal reflux and aspiration of gastric contents during nasogastric feeding: the effect of posture [abstract]. *Int Care Med* 1988;14(suppl 2):296–7.
41 Tryba M. Stress bleeding prophlaxis with sucralfate. Pathophysiological basis and clinical use. *Scand J Gastroenterol* 1990;25(suppl 173):22–33.
42 Brown C, Rees WDW. Drug treatment for acute upper gastrointestinal bleeding. *BMJ* 1992;304:135–6.
43 Gorbach SL. Population control in the small gut. *Gut* 1976; 8:530–2.
44 Driks MR, Craven DE, Celli BR, *et al.* Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. The role of gastric colonisation. *N Engl J Med* 1987;317:1376–82.
45 Daschner F, Kappstein I, Engles I, Reusenbach K, Pfisterer J, Krieg N. Stress ulcer prophylaxis and ventilation pneumonia: prevention by anti bacterial cytoprotective agents. *Infect Control Hosp Epidemiol* 1988;9:59–65.
46 Pingleton SK, Hinthorn DR, Liu CL. Enteral nutrition in patients receiving mechanical ventilation. Multiple sources of tracheal colonisation include the stomach. *Am J Med* 1986;80:827–32.
47 Reusser P, Zimmerli W, Scheidegger D. Marbet GA, Buser M, Gyr K. Role of gastric colonisation in nosocomial infections and endotoxemia: a prospective study in neurosurgical patients on mechanical ventilation. *J Infect Dis* 1989;160:414–21.
48 Tryba M. Risk of acute stress bleeding and nosocomial pneumonia in ventilated intensive care unit patients: sucralfate versus antacids. *Am J Med* 1987;83:117–24.
49 Feistauer SM, Laggner AN, Makristathis A, Georgopoulos A. Influence of stress-ulcer prophylaxis on translocation of bacteria from the intestinal tract in rats. In: *Proceedings of the 3rd Vienna Shock Forum*. Vienna, 1991.
50 Flaherty J, Nathan C, Kabins SA, Weinstein RA. Pilot trial of selective decontamination for prevention of bacterial infection in an intensive care unit. *J Infect Dis* 1990; 162:1393–7.
51 van Saene HKF, Stoutenbeek CP, Hart CA. Selective decontamination of the digestive tract in intensive care patients: a critical evaluation of the clinical, bacteriological and epidemiological benefits. *J Hosp Infect* 1991;18: 261–77.
52 van Saene HKF, Mostafa SM. The place of selective decontamination in the intensive care unit. *Current Opinion in Anaesthesiology* 1991;4:247–52.
53 Kerver AJH, Rommes JH, Mevissen-Verhage. Prevention of colonisation and infection in critically ill patients: a prospective randomized study. *Crit Care Med* 1988;16: 1087–93.
54 Brun-Buisson C, Legrand P, Rauss A, *et al.* Intestinal decontamination for control of nosocomial multi-resistant Gram-negative bacilli: study of an outbreak in an intensive care unit. *Ann Intern Med* 1989;110:873–81.
55 Godard J, Guillame C, Reverdy ME, *et al.* Intestinal decontamination in a polyvalent ICU: a double-blind study. *Int Care Med* 1990;16:307–11.
56 Gastinne H, Wolff M, Lachatre G, Boiteau R, Savy FP. Antibiotic levels in bronchial tree and in serum during selective digestive decontamination. *Int Care Med* 1991; 17:215–8.
57 Ulrich C, Harinck de Weerd JE, Bakker NC, Jacz K, Doornbos L, De Ridder VA. Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU-acquired infections: a prospective randomized study. *Int Care Med* 1989;15:424–31.
58 Vandenbroucke-Grauls CM, Vandenbroucke JP. Effect of selective decontamination of the digestive tract on respiratory infections and mortality in the intensive care unit. *Lancet* 1991;338:859–62.
59 Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma-reduced septic morbidity. *J Trauma* 1989;29: 916–22.
60 Fiddian-Green RG, Baker S. Nosocomial pneumonia in the critically ill: product of aspiration or translocation? *Crit Care Med* 1991;19:763–9.
61 Marston A, Bulkey J, Fiddian-Green RG, eds. *Splanchnic ischaemia and multiple organ failure*. St Louis: Mosby, 1989.
62 Ambrose NS. Incidence of pathogenic bacteria from mesenteric lymph nodes during Crohn's disease surgery. *Br J Surg* 1984;71:623–5.
63 Alexander JW, Boyce ST, Babcock JF, *et al.* The process of microbial translocation. *Ann Surg* 1990;212:496–512.
64 Redan JA, Rush BF, Lysz TW, Smith S, Machiedo GW. Organ distribution of gut-derived bacteria caused by bowel manipulation or ischemia. *J Trauma* 1990;159: 85–90.
65 Moore FA, Moore EE, Poggetti R, *et al.* Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. *J Trauma* 1991;31:629–36.
66 Maynard N, Bihari DJ. Post-operative feeding. Time to rehabilitate the gut. *BMJ* 1991;303:1007–8.
67 Souba W, Herskowitz K, Salloum RM, Chen MK, Austgen TR. Gut glutamine metabolism. *J Parent Ent Nut* 1990; 14(suppl):45–50S.
68 Levine GM, Deren JJ, Steiger E, Zinno R. Role of oral intake in maintenance of gut mass and disaccharide activity. *Gastroenterology* 1974;67:975–82.
69 Alverdy JC, Aoys E, Moss GS. TPN promotes bacterial translocation from the gut. *Surgery* 1988;104:185–90.
70 Shepherd AP. Metabolic control of intestinal oxygenation and blood flow. *Fed Proc* 1982;41:2084–9.
71 Guedon C, Schmitz J, Lerebours E, *et al.* Decreased brush border hydrolase activities without gross morphological changes in human intestinal mucosa after prolonged total parenteral nutrition of adults. *Gastroenterology* 1986;90: 373–4.
72 Greenberg R, Wolman SL, Christofides ND, Bloom SR, Jeejeebhoy KN. Effect of TPN on gut hormone release in humans. *Gastroenterology* 1981;80:988–93.

73 Jacobs SJ, Chang RW, Lee B, Bartlett FW. Continuous enteral feeding: a major cause of pneumonia amongst ventilated intensive care unit patients. *J Parent Ent Nutr* 1990;**14**:353–7.
74 Freedland CP, Roller D, Roller BS, Wolfe BM, Flynn NM. Microbial contamination of continuous drip feeding. *J Parent Ent Nutr* 1989;**13**:18–20.
75 Strumpf M, Tryba M. Possibilities and restrictions of preventive measures—physiological barriers. In: Proceedings of conference on pulmonary infections in the ICU—new possibilities in diagnosis and prevention. Interlaken, 1991.
76 Leu HS, Kaiser DL, Mori M, Woolson RF, Wenzel RP. Hospital-acquired pneumonia. Attributable mortality and morbidity. *Am J Epidemiol* 1989;**129**:1258–67.
77 Rello J, Quintana E, Ausina V, *et al.* Incidence, etiology, and outcome of nosocomial pneumonia in mechanically ventilated patients. *Chest* 1991;**100**:439–44.
78 Rodriguez JL, Gibbons KJ, Bitzer LG, Dechert RE. Pneumonia: incidence risk factors and outcome in injured patients. *J Trauma* 1991;**31**:907–14.
79 Meakins JL, Marshall JCM. The gastro-intestinal tract: the motor of multiple organ failure. *Arch Surg* 1986;**121**: 197–201.
80 Deitch EA, Sittig K, Li M, Berg R, Specian RD. Obstructive jaundice promotes bacterial translocation from the gut. *Am J Surg* 1991;**159**:79–84.
81 Ziegler E, Fisher CJ, Sprung CL. Treatment of Gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. *N Engl J Med* 1991;**324**:429–36.
82 Cohen J, Glauser MP. Septic shock: treatment. *Lancet* 1991;**338**:736–9.
83 Hinds CJ. Monoclonal antibodies in sepsis and septic shock. *BMJ* 1992;**304**:132–3.
84 Dubos R. *Louis Pasteur. Free lance of science.* New York: Da Capo Press, 1950.