Papers and Originals

Necropsy Survey of Staphylococcal Infection on Patients Dying in Hospitals

A Report from the Public Health Laboratory Service*

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Between September 1961 and October 1962 members of a Public Health Laboratory Service working party and their colleagues at a number of hospitals in England and Wales attempted, by means of detailed studies of 595 necropsies, to assess the importance of staphylococcal infection as a cause of death in hospital patients. The survey was prompted by the findings of an earlier one by a P.H.L.S. working party (Report, 1960), in which sepsis proved the undisputed cause of only one death after a series of 3,376 clean operations on surgical patients, although the incidence of post-operative wound infection in these patients was 9.4%.

Relatively little information has been published on the incidence of fatal staphylococcal infections as shown by necropsy surveys. Finland and Jones (1956) isolated "haemolytic *Staphylococcus aureus*," identified by its cultural appearances on sheep's blood agar and not always by a coagulase test, from the heart blood, spleen, lungs, or septic lesions in 266 out of 914 necropsies. Godfrey and Smith (1958) reported the findings on 534 necropsies, in which *Staph. aureus* was thought to be the main cause of death in 20 (3.7%) and a contributory cause in a further 69 (13%). Perrin and McGowan (1960) found evidence of staphylococcal sepsis in 46 (27%) out of 171 necropsies. In 10 of the 46 subjects a confluent staphylococcal bronchopneumonia was thought to be the primary cause of death. In a further 31 subjects staphylococcal sepsis was a major or minor contributory cause of death. During the first five months of the survey, however, a high incidence of staphylococcal deaths was associated with the prevalence of influenza.

Larsen and Jorgensen (1960) found *Staph. aureus* to be the main or sole cause of death in 41 (1%) of 3,926 necropsies. The staphylococcal deaths included 29 hospital infections, of which 16 were post-operative. There were 10 cases of staphylococcal septicaemia and 10 of pyaemia, and in 7 of these 20 generalized infections an acute staphylococcal endocarditis was found. Staphylococcal pneumonia was given as the main cause of death in 11 subjects, and post-operative staphylococcal enterocolitis in 5. Mitchell *et al.* (1961) studied a series of 150 consecutive necropsies. The series included 48 male subjects who had been engaged in dusty occupations. Lung sepsis was found in 40% of the necropsies and in 50% of deaths taking place eight or more days after admission to hospital. Septic lungs that yielded *Staph. aureus* on culture were found in 28 (41%) out of 69 subjects with pre-existing chronic lung disease and in only 19 (24%) out of 81 of the remainder. Finally, Macpherson *et al.* (1963) thought that staphylococcal infection had been the main cause of death in 25 (4.6%) out of 546 necropsies and a contributory cause of death in a further 38 (7%).

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Bacteriologists: Dr. J. F. Archer, Dr. T. D. Brogan, Dr. B. H. E. Cadness-Graves, Dr. J. M. Croll, Dr. D. G. Davies, Dr. E. H. Gillespie, Dr. E. J. G. Glencross, Dr. K. E. A. Hughes,* Dr. M. H. Hughes, Dr. R. I. Hutchinson, Dr. C. H. Jellard, Dr. P. G. Mann, Dr. E. R. Mitchell, Dr. B. Moore,* Dr. R. Pilsworth, Professor R. E. O. Williams,* Dr. P. J. Wormald.

Those marked with an asterisk, together with Dr. H. R. Cayton, Dr. R. J. Henderson, Dr. J. C. McDonald, and Dr. M. T. Parker, constituted the committee which organized the investigation. Dr. Parker was chairman and Dr. Moore was secretary. Dr. Moore analysed the results and prepared the report; reprints may be obtained from him at the Public Health Laboratory, Bradninch Place, Gandy Street, Exeter.

Materials and Methods

Selection of Subjects

Each centre planned to make a detailed study of two necropsies a week. As those who die in hospital are mostly the old, the selections of subjects was so made as to include young patients wherever possible. A group of persons who had died outside hospital were also included, in the hope that the bacteriological findings in these might help to distinguish phenomena associated with terminal illness from those merely reflecting the hospital environment. Each laboratory was asked to include in its series one traumatic and one non-traumatic death monthly in persons who had died outside hospital, and, in addition, all hospital necropsies on children aged 1 month to 15 years. The remainder of the series was to be drawn from the main group of hospital deaths in adults aged 16 and over, but to avoid the deliberate inclusion or exclusion of septic deaths the necropsies chosen for study should be carried out on a fixed day of the week, preferably not Monday. On that day one or two necropsies were selected, with a preference for younger subjects. When two necropsies were not done on this day the following day was acceptable.

Bacteriological Subjects

Swabs were collected from various sites before the organs were removed from the body, either from surfaces or through an incision made with a sterile scalpel into surfaces previously seared with an electric soldering-iron. The sites swabbed and various details of technique were as follows:

1. *Nose.*—A single broth-moistened swab from both nostrils.

2. *Trachea.*—The front of the trachea was seared below the larynx and incised. A swab was pushed caudally through the incision and rubbed against the mucosa near the bifurcation.

3. *Upper and Lower Lobes of Right and Left Lungs.*—The surface of each lung lobe was seared and an incision made to a

depth sufficient to avoid the seared tissues but without penetrating a main bronchus. Swabs were then taken from the depths of the incision.

4. *Neck of Bladder.*

5. *Renal Pelves.*—The pelvis of each kidney was seared and incised before swabbing.

6. *Posterior Vaginal Fornix.*

7. *Ileocaecal Junction.*

8. *Rectum.*

9. *Spleen.*

10. *Any Suppurating Lesion Found.*

Bacteriological Methods

Three requirements were laid down for every necropsy studied—namely, (1) isolation and identification of the causative pathogen from all purulent lesions wherever found ; (2) culture of all swabs for *Staph. aureus ;* and (3) identification of all pathogenic bacteria and of Gram-negative organisms of doubtful pathogenicity that were isolated from lung swabs.

Staph. aureus.—Blood agar was used for the culture of swabs from all sites other than ileocaecal junction and rectum, and all lung swabs were cultured on chocolate agar. Selective media for staphylococci were also used, including 7% salt agar, either with mannitol and an indicator or incorporating phenolphthalein phosphate. All laboratories used their customary routine medium to suppress the swarming of proteus organisms. A record was made of the number of *Staph. aureus* colonies found on primary plates—namely, 1–9 colonies +, 10–99 colonies + +, 100 colonies and over + + +. All staphylococcal strains were examined for sensitivity to penicillin and tetracycline, and were also phage-typed.

Lung Pathogens.—Lung swabs were examined in particular for *Staph. aureus, Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae,* and *Streptococcus pyogenes.*

Other Gram-negative Bacilli from the Lungs.—Gram-negative bacilli of the *Proteus* group and *Escherichia coli* and *Pseudomonas pyocyanea* (*Pseudomonas aeruginosa*) were identified by appropriate methods. All other Gram-negative rods isolated from lung cultures were sent in agar stab culture to the Central Public Health Laboratory, Colindale, and kindly identified for the working party by Dr. K. P. Carpenter.

Necropsy Routine

Details of necropsy routine were left to the consultant pathologist. If for one reason or another the brain was not inspected a note to this effect was made on the record form. Where respiratory infection was included among the causes of death the working party agreed that the lesions should be examined histologically ; in some busy laboratories, however, this was not done.

Records

A record form was completed for each necropsy, giving the relevant clinical and necropsy findings, and including a comment by the pathologist stating whether in his opinion staphylococcal infection had contributed to the death of the patient.

Preliminary Analysis of Survey Findings

Of the 595 record forms completed by 15 participating laboratories the majority came from eight centres, which between them investigated 540 necropsies. The material studied by the major participants represented about 10% of all necropsies done by them during the year. The survey included 470 necropsies on subjects who had died in hospital and 125 on persons who died outside hospital or, in a few instances, in hospital casualty departments before they could be admitted to a ward. This group is referred to hereafter as the B.I.D. (" brought in dead ") group.

The main purpose of the survey was to assess the importance of staphylococcal infection as a cause of death in hospital patients. In examining the individual necropsy record form this assessment resolved itself into an attempt to answer two questions: (1) Did this patient have terminal staphylococcal disease ? (2) If so, would he have survived had the staphylococcal infection not supervened ? The main doubt in answering the first question arose in relation to the complication most often cited—namely, staphylococcal pneumonia. For many of the subjects the second question was also difficult to answer, because of the gravity of their underlying illness, their advanced age, or the presence of other contributory disability.

The final conclusions on each necropsy were usually stated by the pathologist in the form of the customary death certificate, giving immediate and antecedent causes of death and other contributory causes. This information is summarized below for the hospital necropsy series. A distinction was made between underlying and contributory causes of death, and the use of these terms in the remainder of this paper calls for definition and comment.

Underlying Cause of Death.—The pathological condition selected as the underlying cause of death was the disease or injury that initiated the train of morbid events leading directly to death. So defined, the underlying cause of death could range from an inexorably lethal condition like leukaemia in some subjects to a trivial disease followed by a disastrous complication. The trivial disease would in this instance rank as the underlying cause of death.

Contributory Causes of Death.—These were pathological conditions, other than underlying causes as above defined, present at death and thought to have contributed to the death of the patient. In some instances the contributory cause cited was the immediate cause of death—for example, cerebral haemorrhage in a patient admitted to hospital for an unrelated condition. In many others the conditions recorded as contributory causes of death were the usual concomitants of advancing age, such as arteriosclerosis, and their contribution to the patient's death was more difficult to assess. In the context of the present investigation terminal infections such as staphylococcal septicaemia or pneumonia also came under this heading.

Age, Sex, and Morbidity Structure of the Hospital Necropsy Series

The age and sex distribution and the major underlying causes of death of the 470 hospital patients are shown in Table I. The corresponding figures for the B.I.D. group are for convenience given in the same table. Clearly, the spectrum of underlying causes of death differed greatly in the two groups, those brought in from outside for necropsy having been largely acute cardiac, accidental, or suicidal deaths, while the hospital series was heavily weighted with malignant or chronic disease. For 186 of the 470 hospital deaths the underlying cause alone was cited in the pathologist's report. In the remainder one or more contributory causes were found. Thus some patients with malignant neoplasms died of general carcinomatosis, some from the effects on adjacent structures of the primary growth or a metastatic focus, and some of a terminal bronchopneumonia. The infective complications were of particular interest to the present study.

Infection as an Underlying Cause of Death in the Hospital Series

In 11 necropsies in the hospital series an infection was thought to be the underlying cause of death as above defined. Of the 11 eight were admitted to hospital with symptoms of

pneumonia, and the remaining three were suffering from pneumococcal meningitis, meningococcal septicaemia, and varicella pneumonia respectively. Of the eight pneumonias referred to above four were staphylococcal, and they included two subjects in whom the causal staphylococci were antibiotic-resistant hospital strains. In these two, and possibly in others, a hospital cross-infection of the respiratory tract may have been superimposed upon the original infective agent.

TABLE I.—*Age and Sex Distribution and Underlying Causes of Death in the Hospital and B.I.D. Groups*

Underlying Cause of Death	No.	Age 0–4	5–39	40–9	50–9	60–9	70–9	80+
Hospital series								
Malignant neoplasm ..	110 M 66		1	3	12	25	19	6
	F 44		4	4	10	15	8	3
Cardiac	108 M 69	5	5	6	13	17	17	6
	F 39	3	3	4	3	10	11	5
Intestinal	52 M 27		2	3	4	10	5	3
	F 25	3	4	1		6	6	5
Respiratory	40 M 25	2	2	2	4	5	8	2
	F 15		2		2	2	8	1
Cerebral vascular disease	27 M 14			1	3	3	2	5
	F 13		3		2	5	2	1
Arteries and veins, not cerebral	26 M 15		3	1	4	5	1	1
	F 11				1	3	3	4
Genito-urinary tract ..	20 M 11		1		1	3	4	2
	F 9		3				4	2
Injuries	19 M 11	1	5		1	2	1	1
	F 8		1			1	4	2
Diseases of blood and blood-forming organs	19 M 11		1		4	3	3	
	F 8			1	1	3	2	1
Miscellaneous	49 M 29	6	5	4	6	3	4	1
	F 20	2	2		5	6	3	2
Total	470							
B.I.D. Group*								
Cardiac..	59 M 34	2		5	5	10	11	1
	F 25†		1		3	5	12	3
Respiratory	18 M 13	5	2		2	2	2	
	F 5	4				1		
Accidents	14 M 9		4		2	1	1	1
	F 5			2	1		1	1
Poisoning	11 M 5		2			2		1
	F 6		1	1		3	1	
Arteries and veins ..	6 M 3		1				1	1
	F 3					1	2	
Intestinal	5 M 2	2						
	F 3	2						1
Miscellaneous	12 M 9	2	1	1		2	2	1
	F 3	1				2		
Total ..	125							

* Brought in dead. † Age of 1 female unknown.

Infection as a Contributory Cause of Death in the Hospital Series

A full inventory of the infective contributory causes of death found in subjects in the hospital series would include such conditions as peritonitis or chronic pyelonephritis, which, however important, were not the special concern of the working party, and have not been recorded in this report. The principal aim of the survey was to assess the incidence of hospital cross-infection or of infections mediated in some way through the patient having been in hospital rather than at home in the period preceding death. Interest centred mainly on staphylococcal infections, and only for this organism were the typing techniques used sufficiently refined to be of epidemiological value. Infective contributory causes of death in the hospital series are discussed in the following paragraphs under three headings—namely, terminal pneumonias, non-pulmonary staphylococcal complications, and other miscellaneous infections of a specific nature. Their incidence is summarized in Table II, and relevant details of the 41 terminal infections due to staphylococci are listed in Table III.

Terminal Pneumonias

A naked-eye necropsy diagnosis of bronchopneumonia or pneumonia was recorded on 96 out of 470 hospital subjects. Of the 96 only 46 were histologically investigated ; 39 of these were thought to show histological evidence of bronchopneumonia.

The bacterial aetiology of many of the pneumonias was far from clear, and, in particular, the diagnosis of staphylococcal pneumonia was hedged with uncertainty, and requires some comment. Chickering and Park (1919), who had observed fulminating staphylococcal complications of influenza in 1918, thought that staphylococcal pneumonia was a disease characterized by the formation of multiple abscesses in the lungs. A non-suppurative form of the disease has, however, been described. Gresham and Gleeson-White (1957), in a study of terminal staphylococcal bronchopneumonia in debilitated hospital patients, found that in 14 such subjects whose lungs yielded staphylococci in large numbers at necropsy, histological examination showed intact bronchioles and alveolar ducts surrounded by extensive areas of haemorrhagic oedema. The similarity of this picture to that seen in the fulminating staphylococcal pneumonia of influenza epidemics led them to suggest that a non-suppurative form of staphylococcal pneumonia occurred as a terminal process in lungs rendered oedematous either by influenza or by some other pathological mechanism. The demonstration by Powell (1961) of pulmonary vascular lesions in staphylococcal septicaemia is relevant in this context. These lesions were focal haemorrhages due to fibrinoid necrosis of the walls of smaller pulmonary blood-vessels ; they were almost invisible at necropsy and might be overlooked in fixed lungs, but were clearly visible in paper-mounted sections prepared by the method of Gough and Wentworth (1949). The criteria for a confident diagnosis of

TABLE II.—*Incidence of Main Infective Contributory Causes of Death in the Hospital Series*

Underlying Cause of Death	Total No.	No. with *Staph. aureus* in Lungs	Infective Contributory Causes of Death: Terminal Bronchopneumonia: Total Diagnosed Naked-eye	Bacterial Cause Assigned: *Staph. aureus*	*Str. pneumoniae*	Other	Doubtful Aetiology: No.	Other Confirmatory Evidence: Histological	Clinical	Non-pulmonary Staphylococcal Disease: Enterocolitis	Septicaemia	Other	Miscellaneous Non-staphylococcal Infections
Malignant neoplasm	110	33	28	10	4	1*	13	4	5	1		1‡	1¶
Cardiac	108	11	9	2	1		6	4	1			1§	4**
Intestinal	52	13	8	2	1		5		1	3			
Respiratory	40	14	9	1	1		7	4	1				
Cerebral vascular disease	27	6	5		2		3	1					
Arteries and veins, not cerebral	26	8	3	2			1			1			
Genito-urinary tract	20	10	6	3	1		2						
Injuries	19	6	6	4			2						
Diseases of blood and blood-forming organs	19	4	5	1	1		3	1					1††
Miscellaneous	49	17	17	5	4	1†	7		1		3	1‖	
Total	470	122	96	30	15	2	49	14	9	5	3	3	6

* *Str. pyogenes.* † *Ps. pyocyanea.* ‡ Post-operative meningitis. § Empyema following paracentesis. ‖ Exfoliative dermatitis. ¶ *Listeria* meningitis terminating lymphosarcoma. ** Subacute bacterial endocarditis. †† Streptococcal septicaemia terminating leukaemia.

staphylococcal pneumonia at necropsy are, therefore, by no means clear-cut.

The difficulty of diagnosing staphylococcal pneumonia is aggravated by the frequency with which, in this and other necropsy studies, staphylococci have been isolated in quite large numbers from the lungs of subjects with no evidence of pneumonia. In the present hospital series, as shown in Table II, the lungs of 122 subjects yielded staphylococci on culture. Only 30 of these, however, seem to have had a definite pneumonia. In 15 an undoubted suppurative pneumonia was recorded ; these included five localized staphylococcal pneumonias distal to an obstructive carcinoma of bronchus. In a further five the macroscopic extent of the pneumonic process paralleled precisely the isolation of staphylococci from lung-swab cultures. For the remaining 10 the diagnosis seemed beyond dispute when other relevant findings were taken into account—for example, the presence of undoubted staphylococcal lesions elsewhere in the body, the histological picture, collateral naked-eye evidence, such as the presence of pleurisy, and the bacteriological findings. The 30 subjects with staphylococcal pneumonia are listed as Cases 1–30 in Table III.

The hospital series also included 15 pneumococcal pneumonias, one pneumonia caused by a group A streptococcus, and one apparently due to *Ps. pyocyanea*. For the remaining 49 pneumonias the causal agent remains uncertain, partly no doubt because of chemotherapy. Of the 49 14 gave a histological picture of bronchopneumonia and a further nine a clear clinical history of terminal pneumonia. How many additional true pneumonias were missed because of indefinite naked-eye appearances can only be matter for speculation.

Non-pulmonary Staphylococcal Complications

Details of 11 subjects whose deaths were caused or accelerated by non-pulmonary staphylococcal complications are given in Tables II and III. Of these, five had staphylococcal enterocolitis due to antibiotic-resistant staphylococci falling into phage types associated with hospitals. All five patients had been operated upon, all had received broad-spectrum antibiotics ; four of the five had been given tetracycline. In each case the causative organism was resistant to the antibiotic given.

Three subjects died of staphylococcal septicaemia. One of these (Case 36) was a patient with psoriasis on corticosteroid therapy who became infected in hospital with an antibiotic-resistant staphylococcus. The other two patients, one a diabetic and the other suffering from skin sepsis, had septicaemia when admitted to hospital.

The remaining three staphylococcal deaths in hospital subjects were the result respectively of post-operative meningitis following hypophysectomy for carcinoma of the breast, empyema after paracentesis of the pleural cavity in a patient with heart disease, and generalized staphylococcal dermatitis in a patient with mycosis fungoides.

Miscellaneous Infections

Miscellaneous non-staphylococcal infections contributing to death included four cases of subacute bacterial endocarditis, a terminal listerial meningitis in a patient with lymphosarcoma, and a terminal streptococcal septicaemia in a patient with lymphatic leukaemia (see Table II).

TABLE III.—*Pathological, Bacteriological, and Clinical Details of Hospital Subjects with Staphylococcal Sepsis as Contributory Cause of Death*

Case No.	Age and Sex	Underlying Cause	Staphylococcal Complication	Drug Sensitivity		Phage-typing Pattern	Other Relevant Clinical and Pathological Findings
				Pen.	Tet.		
1	67 M	Carcinoma of Bronchus	Pneumonia	R	R	83A	
2	70 M	,, ,, ,,	,,	S	S	3A	
3	70 M	,, ,, ,,	,,	R	R	80/81	
4	70 M	,, ,, ,,	,,	S	S	52+	
5	56 M	,, ,, ,,	,,	R	R	80/81	
6	54 M	,, ,, ,,	,,	S	S	80/81	Diabetes mellitus
7	69 F	Carcinoma of oesophagus	,,	R	R	75/77	Oesophageal perforation after oesophagoscopy
8	53 M	Carcinoma of larynx	,,	S	R	80/81	Tracheostomy. Old myocardial infarct
9	55 M	Cerebral tumour	,,	S	S	71	Pulmonary embolism. Thrombosis leg veins
10	58 F	,, ,,	,,	R	S	75/77	
11	68 F	Myocardial ischaemia	,,	R	S	81	Fibrinous pericarditis. R. hemiplegia
12	76 M	Chronic heart block	,,	R	R	80/81	Thrombosis of common iliac. Gangrene of foot
13	86 M	Intestinal obstruction	,,	R	R	80/81	
14	64 M	Anastomotic ulcer	,,	R	R	83A	Post-operative perigastric abscess. Ileus
15	72 M	Chronic bronchitis	,,	R	R	80/81	Peripheral neuritis
16	55 F	Atherosclerosis and gangrene of foot	,,	R	S	6/7/47/53/54	Spreading cellulitis from foot
17	81 F	Femoral venous thrombosis-pulmonary embolism	,,	R	R	52/52A/80	Bronchiectasis
18	80 M	Hydronephrosis. Prostate	,,	S	S	29	Uraemia. Cerebral softening. Diverticula of bladder
19	64 M	Pyonephrosis	,,	S	S	53/77	Empyema. Prostate
20	72 M	Pyelonephritis	,,	R	S	55/71	Parkinson's disease. Prostate. Myocardial degeneration
21	80 M	Fractures and multiple injuries	,,	R	R	80/81	
22	81 F	Fractured femur	,,	S	R	6/7/47	
23	74 F	,, ,,	,,	R	R	77	Post-operative ileus
24	64 M	Fracture of skull	,,	R	R	75/77	
25	63 F	Rheumatoid arthritis. Aplastic anaemia	,,	R	S	42E	
26	57 F	Paget's disease of skull	,,	R	R	53/75/77	Platybasia
27	59 M	Cirrhosis of liver	,,	S	S	3B/3C/55	
28	83 M	Polyneuritis	,,	R	R	7/47/54/75	Hypertensive heart disease
29	6/52 M	Recurrent cyanotic attacks	,,	R	R	80/81	
30	81 F	Rheumatoid arthritis	,,	R	R	80/81	Bedsores. Lung abscesses
31	15 M	Perforation of ileum. Old post-operative adhesions	Post-operative enterocolitis	R	R	7/47/53/54/75/+	Peritonitis. Treated with chlortetracycline
32	56 M	Carcinoma of larynx	,, ,,	R	R	75/77	Had laryngectomy. Treated with tetracycline
33	45 M	Gastric ulcer	,, ,,	R	R	52/52A/80	Treated with tetracycline
34	85 F	Acute appendicitis	,, ,,	R	R	7/47/53/54/81/+	Diabetes. Treated with tetracycline
35	62 M	Thrombosis of right iliac artery	,, ,,	R	R	83A	Treated with erythromycin and chloramphenicol
36	67 F	Psoriasis	Septicaemia	R	R	77	Corticosteroid therapy. Sepsis at site of i.v. drip. Steroid diabetes
37	51 F	Boil of abdomen	,,	S	S	29/52/80	Congenital heart disease. Hemiplegia
38	51 M	Diabetes	,,	S	S	Not typable	
39	58 F	Carcinoma of breast; hypophysectomy	Post-operative meningitis	R	S	52A/79	
40	48 M	Myocardial fibrosis due to coronary disease	Empyema after paracentesis	R	R	6/47/42E/53/77/+	
41	68 F	Mycosis fungoides	Exfoliative dermatitis	R	R	47/77/+	

R = Resistant. S = Sensitive.

Bacteriology of the Lungs at Necropsy

Staph. aureus

As shown in Table II, 122 (26%) out of 470 hospital subjects yielded staphylococci on direct culture of one or more lung swabs taken at necropsy. Of these only 30 were thought to have had staphylococcal pneumonia. The necropsy records of the hospital series were scrutinized for any factor that might explain these findings. This was done in three ways: (1) by comparing the laboratory results obtained on the B.I.D. group with those obtained on subjects who died in hospital; (2) by seeking an association between the finding of staphylococci in the lungs and such factors as the duration of stay in hospital before death, the duration of coma before death, and the interval between death and necropsy; and (3) by relating the isolation of staphylococci from the lung to the cultural findings on swabs from other sites.

Only 6 (4.8%) out of 125 in the B.I.D. group had staphylococci in the lungs, and it was notable that four of the six had recently been in hospital, and in three of the four the staphylococcus isolated from the lungs was an antibiotic-resistant hospital strain. Thus the isolation of staphylococci from the lungs was clearly associated with death in hospital. Whether this multiplication of staphylococci took place (1) during the patients' stay in hospital, (2) as a terminal event, or (3) in the interval between death and necropsy could not be determined from the bacteriological findings alone. Post-mortem multiplication seemed improbable on various grounds. First, nearly all the cadavers were refrigerated while awaiting necropsy. Again, the proportion of lung positives was unaffected by increasing duration of the interval between death and necropsy. Finally, had the multiplication of staphylococci in the lungs occurred after death, a higher proportion of positive findings would have been expected in the B.I.D. group.

There was also no indication of an agonal multiplication of staphylococci. The clinical histories of 134 subjects in the hospital series, excluding patients with terminal pneumonia, were detailed enough to permit grading of the acuteness of death as sudden, taking up to three days, or occurring after more than three days of coma. The proportions of subjects in these three subgroups from whose lungs staphylococci were isolated at necropsy were virtually identical. The duration of the terminal phase did not, therefore, determine the incidence of staphylococci in necropsy lung-swab cultures.

All the evidence points to the third possibility, that colonization of the lungs with staphylococci had occurred in the course of some patients' stay in hospital. The bacteriological findings on hospital subjects for whom pneumonia was not given as a cause of death show a steady increase in the carrier rates for staphylococci at various sites with increasing duration of stay in hospital. Thus the numbers of staphylococcal carriers in the nose, lungs, and lower intestine, according to whether the subjects in question had been in hospital for less than a week or for a week or more before death, were as follows:

In Hospital	Total	Nose +	Lung +	Gut +
Less than a week ..	181	67 (37%)	24 (13%)	12 (6·6%)
A week or more ..	185	92 (50%)	45 (24%)	26 (14%)

The increase in nasal carriage of staphylococci by hospital patients has often been described. The foregoing findings support the suggestion of Emson (1964) that hospital patients may also become bronchial carriers of *Staph. aureus*.

Str. pneumoniae

Pneumococci were isolated from one or more lung lobes of 29 subjects in the hospital series. The isolation of pneumococci, in sharp contrast with the staphylococcal findings discussed above, was closely correlated with the presence of lung disease. From the 366 hospital subjects for whom pneumonia was not cited as underlying or contributory cause of death, the number of pneumococcal isolations was only 12, and 7 of the 12 had organic or traumatic pulmonary lesions.

H. influenzae

H. influenzae was isolated from the lungs of 16 hospital subjects, of whom six also had pneumococci in the lungs.

Gram-negative bacilli

Gram-negative rods, mostly enterobacteria, were isolated from one or more lung lobes of 165 (35%) out of 470 hospital subjects and of 16 (13%) out of 125 in the B.I.D. group.

Of the 165 subjects in the hospital series from whose lungs Gram-negative rods were isolated 95 yielded *E. coli*, 22 *Proteus mirabilis*, 13 other *Proteus strains*, 12 *Klebsiella*, 5 *Citrobacter*, and a few yielded enterobacteria of other types. In addition, *Ps. pyocyanea* was isolated from the lungs of 10 subjects.

No relation could be demonstrated between the isolation of coliform organisms from the lungs and a history of treatment with penicillin, tetracycline, other antibiotics, or corticosteroids. In many of the subjects from whose lungs coliform organisms were isolated, however, these organisms may not have been irrelevant contaminants. Many of the patients had abdominal lesions from which systemic dissemination of coliform organisms might have taken place. Again, in 139 of the 165 subjects whose lungs yielded Gram-negative rods at necropsy only one bacterial species was recorded. This high proportion may be fallacious, because of failure to examine a sufficient number of colonies on different cultures, and also because of the serological diversity that the recording of an isolation of *E. coli* may conceal. Nevertheless, it was notable that, of the subjects in this group whose lungs failed to yield *E. coli* on culture, the lungs of 32 gave a growth from two or more lobes of organisms that, so far as the biochemical tests done on them could demonstrate, were of one enterobacterial species. From the lungs of a further eight subjects *Ps. pyocyanea* was the only Gram-negative rod isolated. These findings are somewhat incompatible with a random flooding of the lungs with gut organisms before or after death.

Discussion

The 470 subjects in the hospital series probably constituted a fair sample of the necropsy material examined at general hospitals in England and Wales during the year September 1961 to October 1962. The information on the record forms suggested that, in at least 41 (8.6%) of the 470, staphylococcal sepsis was a contributory cause of death and the terminal event in the clinical history. The staphylococcal deaths included 30 from pneumonia, five from enterocolitis, three from septicaemia, two post-operative infections, and one generalized dermatitis.

The first question posed by these findings was whether the 41 staphylococcal deaths should rank as preventable disasters or whether many were simply a mode of dying in patients who, for one reason or another, had little hope of recovery from their underlying disease. The main pertinent facts have been listed in Table III. Ten patients (Cases 1–10) had malignant disease terminated by staphylococcal pneumonia. In 3 of the 10, pathological conditions other than the neoplasm and the terminal pneumonia were also recorded. In one patient (Case 7), who had carcinoma of the oesophagus, the pneumona followed an accidental perforation of the oesophagus and stomach at oesophagoscopy. How much the staphylococcal pneumonia curtailed life in these 10 subjects with malignant disease is

difficult to assess; certainly in some it brought a merciful termination to hopelessly advanced disease.

Of the remaining 20 subjects listed in Table III who had a terminal staphylococcal pneumonia it will be seen that 11 were over 70 years of age and seven were over 80. Seven of the subjects had advanced underlying disease with little prospect of recovery (Cases 11, 12, 18, 19, 20, 25, and 27). Ten others (Cases 13, 15, 17, 21, 22, 23, 24, 26, 28, and 30) were suffering from a severe primary illness or injury, and the part played by staphylococcal pneumonia in their deaths remains in doubt. Three subjects who, on the information given in Table III, might confidently have been expected to survive were Nos. 14, 16, and 29. One (Case 16) was a woman of 55 who developed a patch of discoloured skin on the dorsum of her right foot. After a biopsy the foot became gangrenous and the patient bedridden. Four months later she was admitted to hospital for arterial surgery as her right femoral artery was impalpable, but died within a few days. Another (Case 29) was born in a maternity unit where infections with type 80/81 staphylococci were occurring. The infant was sent home at the usual time after delivery but was readmitted a month later with a history of recurrent cyanotic attacks and the somewhat improbable clinical diagnosis of pertussis. The third subject (Case 14) was a man aged 64 with a 19-year surgical history dating from an operation for the repair of a perforated duodenal ulcer. He was admitted to hospital with a perforated anastomotic ulcer. After a difficult operation he developed a large perigastric abscess and a clinically diagnosed staphylococcal pneumonia, both due to an antibiotic-resistant type 83A staphylococcus.

Eleven patients (Cases 31–41 of Table III) died of staphylococcal infections other than pneumonia. The five cases of staphylococcal enterocolitis (Cases 31–35) had all been given broad-spectrum antibiotics in hospital, and to that extent their deaths might have been prevented. One (Case 34), however, was a diabetic aged 85, and another (Case 31) required broad-spectrum antibiotics because of peritonitis following an ileal perforation. Finally, three subjects (Cases 36, 38, and 40) would probably not have died when they did had they not been infected during operation or instrumentation.

To sum up, it is difficult to estimate accurately the number of preventable deaths from staphylococcal infection among the hospital patients in this survey. The number probably lies somewhere between 10 and 22, and includes between three and 13 cases of pneumonia, at least three cases of enterocolitis, and four other cases of sepsis. Staphylococcal infection may therefore have been responsible for between 2.1 and 4.7% of deaths in hospital patients.

Drug Sensitivity

Another aspect of the hospital staphylococcal deaths requires further scrutiny. Many of the infections recorded in Table III were caused by "epidemic" types of staphylococcus resistant to penicillin and tetracycline and falling into phage types, such as 80/81 and 83A, known to be associated with hospitals. Of the 41 infections listed in the Table 24 were caused by staphylococci resistant to penicillin and tetracycline, two by penicillin-sensitive and tetracycline-resistant strains, six by penicillin-resistant and tetracycline-sensitive strains, and only nine by antibiotic-sensitive staphylococci. Therefore a high proportion of the subjects in the hospital series whose deaths were precipitated by staphylococcal sepsis probably acquired the infecting organism while in hospital. It is pertinent to inquire whether these hospital-acquired organisms might have accelerated the deaths of the patients in question (1) by making effective chemotherapy more difficult, (2) by possessing greater virulence, or (3) by increasing the likelihood of acquisition of staphylococci and therefore of terminal staphylococcal disease in subjects debilitated as a result of injury or organic disease. These questions are considered first in relation to the staphylococcal pneumonias and then in relation to the 11 subjects with other forms of staphylococcal sepsis.

Of the 30 subjects with staphylococcal pneumonia 12 received no antibiotics and five were given antibiotics to which the infecting organisms would have been expected to respond. The remaining 13 were treated with antibiotics to which the strains they harboured were resistant. It therefore seems that most of the patients had not received the antibiotics which might have been expected to control their infections, but it is difficult to estimate how many would have survived if they had received more appropriate treatment.

Barber (1963) suggested that the method by which drug-resistant strains of *Staph. aureus* have been selected in hospitals has tended to select highly virulent organisms, and a study of her own material indicated that at any rate some multiple-resistant staphylococci were of high virulence. No clear information on this point could be expected from the present investigation, but the evidence, such as it was, did not indicate unusual virulence of the hospital strains. First, the proportion of terminal staphylococcal pneumonias in the hospital series due to penicillin- and tetracycline-resistant staphylococci corresponded precisely with the relative frequency of these organisms in the noses of subjects in the hospital series. Secondly, the proportion of subjects with multiple-resistant staphylococci in the nose who contracted pneumonia caused by these strains was certainly no higher than the corresponding proportion for hospital subjects carrying antibiotic-sensitive staphylococci in the nose. If the acquisition of staphylococci in the nose be looked on as an indicator of exposure to hospital organisms, one might have expected a higher incidence of staphylococcal pneumonia in subjects acquiring antibiotic-resistant strains in the nose, had such strains been of heightened virulence.

Finally, to take the third possibility mentioned above, the bronchial carrier rate of staphylococci appeared to increase with duration of stay in hospital. To the extent that organisms acquired in hospital contributed their quota to this increase, some of the subjects in the present series might perhaps have escaped a terminal staphylococcal pneumonia had they not been exposed to the hospital environment.

Little more need be said in this context of the 11 staphylococcal deaths not due to pneumonia. All five staphylococcal strains causing enterocolitis were resistant to penicillin and tetracycline, and the development of the lethal complication was associated with the administration of a broad-spectrum antibiotic. Of the six remaining cases of staphylococcal sepsis three were caused by penicillin- and tetracycline-resistant strains. None of the three received appropriate antibiotics. Possibly one subject (Case 40) might have survived had the correct antibiotic been given, but this is unlikely, as death occurred within 24 hours of onset of the complication.

Bacteriological Questions

The survey raised many bacteriological queries that need further study. First, if a high proportion of patients in hospital are bronchial carriers of staphylococci, the diagnosis of staphylococcal pneumonia by sputum examination is clearly fraught with difficulties. Serial quantitative sputum cultures on the lines suggested by Louria (1962) might help to resolve these difficulties. Further critical necropsy studies on the bronchial carriage of staphylococci are being planned by some members of the present committee.

The significance of the isolation of enterobacteria from the lungs at necropsy also requires further study. As already mentioned, many of the present survey findings were difficult to explain in terms of random contamination of the lungs—for example, by regurgitation and aspiration of vomit or by agonal invasion of the blood-stream by gut organisms. In many of the subjects necropsy confirmed the presence of lesions of the intestinal or genito-urinary tracts from which a blood-

borne invasion by Gram-negative organisms might have occurred. In Adamson's (1949) careful necropsy study of lymph-nodes coliform strains isolated from different parts of the body were usually antigenically alike, and the isolation of such organisms was often associated with intra-abdominal disease. He isolated proteus organisms, for instance, from lymph-nodes at 14 necropsies, and reported that seven of the subjects concerned had had gastro-intestinal disease and a further four had renal infections. Again, Brooke and Slaney (1958), observing the occasional development of jaundice after colonic excision for ulcerative colitis, showed that in patients with this condition portal bacteraemia could often be demonstrated. Finally, the numerous reports in recent years on acute bacteraemic shock in prostatectomy patients have also drawn attention to blood-borne invasion by enterobacteria, and, indeed, raise the query whether some of the subjects in the present necropsy series may not have died as a result of unsuspected bacteraemic shock.

Summary

A combined pathological and bacteriological necropsy study was made between September 1961 and October 1962 at a number of general hospitals in England to find the incidence of deaths in hospital from staphylococcal infection.

The survey covered 470 subjects who had died in hospital, and a control group of 125 necropsies on persons who had died outside hospital. The major part of the work was done at eight centres.

In all, 41 (8.6%) of the 470 hospital subjects had staphylococcal sepsis as the immediate cause of death. They included 30 with staphylococcal pneumonia, five with enterocolitis, three with septicaemia, two others with sepsis after operation or needling, and one with exfoliative dermatitis. In many instances staphylococcal pneumonia was a terminal event in patients who would not have been expected to survive. Probably, however, between 2.1 and 4.7% of the patients would not have died when they did if they had not acquired a staphylococcal infection.

In at least three of the five deaths due to enterocolitis the administration of a broad-spectrum antibiotic probably led to the patient's death.

Staph. aureus and coliform organisms were isolated from a large proportion of lungs at necropsy. The significance of these findings is discussed.

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Role of Airborne Transmission in Staphylococcal Infections*

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The importance of physical contact, especially via the hands of personnel, in the spread of staphylococci to newborn infants has been indicated in previous studies from this hospital (Wolinsky *et al.*, 1960; Mortimer *et al.*, 1962). The results of one of these trials (Mortimer *et al.*, 1962) suggested that the airborne route was relatively unimportant. However, because the study nursery was small and there was less than optimum supervision of the nurses attending the infants, it was impossible to draw definite conclusions concerning the relative importance of airborne organisms in the transmission of staphylococci in the nursery. The present study was designed to define the importance of this route.

Materials and Methods

Eight bassinets were placed in a special room 16 by 18 ft. (4.9 by 5.4 m.) in two groups of four each, one group at each end of the room (see Diagram). A line was marked on the floor to separate the two groups. The four bassinets at the far end of the room were occupied by infants admitted direct from the delivery-room. These infants were designated AB (airborne) babies. They were retained in these positions until they were discharged from the hospital, usually when 3 to 5 days old, or until a culture positive for *Staphylococcus aureus* was recognized, at which time they were transferred to the main nursery. At the near end of the room two positions were reserved for X (index) babies. These were infants who had become naturally colonized in the nose or umbilicus, or both, with typable strains of *Staph. aureus* in the main nurseries of the hospital but who did not show overt signs of infection. In the other two positions close to the index babies were placed infants admitted direct from the delivery-room and designated T (physical transfer) babies. To eliminate the chance of infection during circumcision, only female infants were admitted to the AB and T positions.

The study nursery was staffed by eight special nurses who were divided into two groups, one to care for the AB babies and the other to care for the X and T babies. Every effort was made to prevent the members of one nursing group from having contact with the members of the other group. They were not permitted to cross the line dividing the nursery except to enter and leave and to wash at the sink at the far end of the room. A few of the special nurses were temporary or

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