Contemporary Themes

Septicaemia in the Neutropenic Patient

K. ATKINSON, H. E. M. KAY, T. J. McELWAIN

British Medical Journal, 1974, 3, 244-247

Summary

A total of 29 cases of septicaemia proved by blood culture in 22 severely neutropenic patients with acute leukaemia or aplastic anaemia have been studied. The recovery rate was 75% in the Gram-positive septicaemias and 60% in the Gram-negative septicaemias in which treatment response could be evaluated. Neutropenia predisposed to septicaemia and its degree seemed to be important. The underlying state of the bone marrow was an important prognostic factor; the neutrophil count at the time of diagnosis and the infecting organism were less important. Gentamicin was the single most useful antibiotic, and the infection was controlled largely with gentamicin and one other antibiotic, most often carbenicillin. Possibly a similar result could have been obtained with gentamicin alone, but since the bacterial flora in a given environment is changeable empirical antibiotic regimens should remain flexible.

Introduction

Neutropenia is common during the course of acute myelogenous leukaemia (A.M.L.) and aplastic anaemia and to a less extent acute lymphoblastic leukaemia (A.L.L.). Neutropenia predisposes to bacterial infection, and this often contributes to death.¹ We present here an analysis of the septicaemia seen in one year on one ward with particular reference to the role of neutropenia in predisposing to the infection and to the roles of neutropenia, the underlying state of the bone marrow, and the infecting organism to the outcome of the infection.

Patients and Methods

Altogether 22 patients were studied, 20 with A.M.L., A.L.L., acute undifferentiated leukaemia (A.U.L.), or aplastic anaemia; 1 with lymphosarcoma cell leukaemia; and 1 with advanced hairy cell leukaemia (leukaemic reticuloendotheliosis). All were inpatients of the reverse barrier unit at this hospital. When a pyrexia of 101° F (38.3° C) or above occurred the following procedure was carried out: careful physical examination, blood

culture (5 ml blood in 50 ml glucose broth, 3 ml in 20 ml broth in a Castaneda's medium bottle, and 1 ml in 10 ml Robertson's meat broth), examination of a midstream specimen of urine, and chest x-ray examination. To qualify for analysis the patient had to have a temperature of at least 101° F (38.3° C) at two consecutive four-hourly readings or 101° F on two occasions within 48 hours or 102° F (38.9° C) or above on one occasion. Episodes of pyrexia occurring less than three days apart were analysed together.

If the patient was clinically well and showed no evidence of local infection antibiotics were not given. Further blood samples were taken for culture and a decision on the use of antibiotics was made according to the subsequent temperature, clinical state, and the results of investigations. If the patient was clinically ill intravenous antibiotics were started as soon as the blood samples had been obtained. Gentamicin and carbenicillin were usually used empirically at first and given intravenously as separate bolus injections and short infusions respectively. The dose of gentamicin was 0.8 mg/kg eight-hourly and of carbenicillin 5 g four-hourly for adults and 100 mg/kg six-hourly for children. Cloxacillin was added if evidence of skin or subcutaneous sepsis was present but other antibiotics were used only after in-vitro sensitivities were known. Probenecid was routinely given when a penicillin was used.

Septicaemia was diagnosed only in patients who were clinically ill and from whom blood organisms were cultured at the time of the illness. For the diagnosis to be accepted Gram-positive organisms had to be grown from at least two out of three bottles per set but Gram-negative organisms from only one out of three bottles per set. Patients were judged to have made a complete recovery when they became afebrile and all signs of infection had disappeared.

Results

In 1972, 29 septicaemias were diagnosed in 22 patients. Six patients had two episodes at different times and one had a single episode with two organisms. (Details of the infecting organisms and a summary of the clinical and laboratory findings are set out in tables I and II). Some 60% of the bacterial septicaemias were due to Gram-negative organisms, but 40% were due to Gram-positive organisms, and these therefore, constituted a significant and important group. *E. coli* was by far the commonest Gram-negative organism, *Ps. aeruginosa* accounting for only 12.5%. This was in contradistinction to the findings in 1971 when pseudomonads were the commonest Gram-negative organisms, though the total numbers were much smaller. Four pseudomonal septicaemias were diagnosed in 1971 out of a total of 14 bacterial septicaemias, 10 of which were Gram-negative. In 1973 the pattern was mixed: in the first five months there was no pseudomonal septicaemias and indeed only two pseudomonal infections occurred, one skin infection and one

Leukaemia Unit, Institute of Cancer Research, Royal Marsden Hospital, Sutton, Surrey

K. ATKINSON, M.B., M.R.C.P., Lecturer in Medicine
H. E. M. KAY, M.D., F.R.C.PATH., Consultant Clinical Pathologist
T. J. McELWAIN, M.B., M.R.C.P., Consultant Physician

chest infection. In the last seven months of that year, however, there were four pseudomonal septicaemias as well as six cases of cellulitis, two of urinary tract infection, and one case of meningitis due to *Ps. aeruginosa*.

The reason for the increase in the number of septicaemias in 1972 over 1971 was thought to be the appreciable increase in the duration of neutropenia experienced by patients on the unit in 1972. In table III this is expressed in terms of neutropenic patient-weeks at neutrophil counts of 1,000/mm³ less, 500/mm³ or less, and 100/mm³ or less. Counts of less than 100/mm³ always meant a total absence of neutrophils in the blood. All diseases (A.M.L., A.L.L., A.U.L., and aplastic anaemia) are included together in table III but, in fact, the increase between 1971 and 1972 was due mainly to patients with A.M.L., the duration of total patient-neutropenia being almost doubled in

TABLE III—Duration of Neutropenia (expressed in Weeks) Experienced by Patients on Unit in 1971 and 1972. Approximate Times in Years are shown in Parentheses

Neutrophils/mm ³ :	501-1,000	101-500	0-100
Duration in 1972 ..	292 (5½)	230 (4½)	123 (2½)
Duration in 1971 ..	207 (4)	137 (2½)	46

TABLE I—Organisms causing 29 Septicaemias in 22 Patients during 1972

				No. of Septicaemias
Gram-negative	<i>Escherichia coli</i>	..	..	12
	<i>Pseudomonas</i> sp.	..	..	2
	<i>Klebsiella</i> sp.	..	..	1
	<i>Enterobacter cloacae</i>	..	..	1
Total				16
Gram-positive	<i>Staphylococcus aureus</i>	..	..	4
	<i>Streptococcus viridans</i>	..	..	3
	Beta-haemolytic streptococcus	..	..	2
	<i>Staphylococcus albus</i>	..	..	1
	<i>Bacillus subtilis</i>	..	..	1
Total				11
<i>Candida albicans</i>	..	..	..	2
Grand total				29

this disease. This is simply a reflection of the more intensive therapy to which patients with A.M.L. are now subjected and the fact that to obtain a remission with the chemotherapeutic agents used—cytarabine and daunorubicin—the bone marrow of most patients is rendered temporarily hypoplastic.

In most cases (22 septicaemias; 76%) septicaemia developed when the neutrophil count was 100/mm³ or less. Of the remainder three developed when the count was between 100 and 500/mm³ and four when the count was between 500 and 1,000/mm³. Septicaemia occurred in five out of seven patients (71%) with A.L.L. who had a neutrophil count of less than 100/mm³, whereas in three patients with A.L.L. whose neutrophil count never dropped below 100/mm³ septicaemia did not occur. The difference was less marked in A.M.L. though the trend was the same: septicaemia occurred in 7 but of 20 patients (35%) with A.M.L. whose neutrophil count fell below 100/mm³ at some time during their admission, whereas only one out of four patients whose neutrophil count remained greater than 100/mm³ developed septicaemia.

In 23 of the 27 bacterial septicaemias treatment response could be evaluated (of the other four, two developed candida septicaemia and two received no treatment). The overall re-

TABLE II—Clinical and Laboratory Data on 22 Patients among whom 29 Septicaemias occurred during 1972

Case No.	Age (Yr)	Diagnosis	Marrow Status	Infecting Organism	Neutrophil Count at Time of Positive Body Culture (mm ³)	Antibiotics Used	Treatment Response	Neutrophil Count at Time of Death or Recovery (mm ³)
1	9	A.L.L.	Drug-resistant leukaemia	<i>E. coli</i>	0	Gent., Carb.	Nil	0
2	14	A.L.L.	Newly diagnosed leukaemia	<i>E. coli</i>	40	Gent., Carb.	Complete Recovery	130
3	4	A.L.L.	Newly diagnosed leukaemia/drug-induced marrow hypoplasia	<i>E. coli</i>	0	Gent., Carb.	Complete recovery	
4	43	L.R.E.	Drug-resistant leukaemia	<i>E. coli</i>	56	Gent., Carb.	Nil	0
5	29	L.C.L.	Newly diagnosed leukaemia/drug-induced marrow hypoplasia	<i>Ent. cloacae</i>	0	Gent., Carb.	Complete recovery	0
6	58	A.L.L.	Newly diagnosed leukaemia/drug-induced marrow hypoplasia	<i>Staph. aureus</i>	0	Gent., Carb.	Nil	100
7	46	A.A.	Severe	<i>Staph. aureus</i>	0	Gent., Carb.	Nil	0
8	46	A.A.	Severe	<i>E. coli</i>	0	Gent., Carb.	Nil	0
9	29	A.A.	Severe	<i>Staph. aureus</i>	0	Gent., Carb., Clox.	Complete Recovery	0
10	29	A.A.	Severe	<i>Klebsiella</i> sp.	0	Gent., Carb.	Nil	0
11	8	A.A.	Mild	<i>Staph. aureus</i>	700	Gent., Clox.	Complete recovery	1,000
12	6	A.L.L.	Drug-resistant leukaemia	<i>Str. viridans</i>	96	Pen.	Complete recovery	
13	4	A.A.	Severe	<i>Str. viridans</i>	32	Pen., Amp.	Complete recovery	180
14	61	A.M.L.	Newly-diagnosed leukaemia	β -Haem. strep.	600	Gent., Carb., Pen.	Complete recovery	180
15	61	A.M.L.	Drug-induced marrow hypoplasia	β -Haem. strep.	0	Amp., Clox.	Not evaluable (candida septicaemia developed)	
16	25	A.U.L.	Drug-induced marrow hypoplasia	<i>Staph. albus</i>	0	Gent., Carb., Clox.	Not evaluable (candida septicaemia developed)	
17	25	A.U.L.	Drug-induced marrow hypoplasia	<i>C. albicans</i>	0	Gent., Carb., Clox., Amphotericin	Nil	0
18	29	A.U.L.	Drug-induced marrow hypoplasia	<i>Bacillus</i> sp.	90	Nil	Not evaluable (recovered spontaneously)	0
19	61	A.M.L.	Newly diagnosed leukaemia	<i>E. coli</i>	790	Gent., Carb.	Complete Recovery	168
20	61	A.M.L.	Drug-resistant leukaemia	<i>E. coli</i>	115	Nil	Not evaluable (died without treatment)	
21	47	A.M.L.	Newly diagnosed leukaemia/drug-induced marrow hypoplasia	<i>E. coli</i>	0	Gent., Carb.	Complete recovery	528
22	47	A.M.L.	Drug-resistant leukaemia	<i>E. coli</i>	0	Gent.	Complete recovery	1,500
23	59	A.M.L.	Drug-induced marrow hypoplasia	<i>E. coli</i>	0	Gent., Carb., Cep.	Complete recovery	1,000
24	3	A.M.L.	Drug induced marrow hypoplasia	<i>E. coli</i>	0	Gent., Cep.	Complete recovery	272
25	29	A.A.	Severe	<i>E. coli</i>	0	Gent., Cep.	Nil	0
26	35	A.M.L.	Drug-resistant leukaemia	<i>Pseudomonas</i> sp.	0	Gent., Carb.	Nil	0
27	51	A.M.L.	Drug-resistant leukaemia	<i>Pseudomonas</i> sp.	308	Gent., Carb.	Complete recovery	1,076
28		A.M.L.	Drug-induced marrow hypoplasia	<i>C. albicans</i>	180	Amp., Clox. (for β -haem. strep.)	Not evaluable (no anticandida treatment)	0

L.R.E. = Leukaemic reticuloendotheliosis (chronic hairy cell leukaemia). L.C.L. = Lymphosarcoma cell leukaemia. A.A. = Aplastic anaemia. Gent. = Gentamicin. Carb. = Carbenicillin. Cep. = Cephalothin. Clox. = Cloxacillin. Pen. = Penicillin. Amp. = Ampicillin. β -haem. strep. = Beta-haemolytic streptococcus.

TABLE IV—Outcome of Septicaemia in relation to Infecting Organism (1972)

	No. of Septicaemias	No. Fatal	No. Non-fatal
Gram-negative organisms	16	7	9
<i>E. coli</i> ..	12	5	7
<i>Pseudomonas</i> sp. ..	2	1	1
<i>Klebsiella</i> sp. ..	1	1	0
<i>Ent. cloacae</i> ..	1	0	1
Gram-positive cocci ..	8	2	6
<i>B. subtilis</i> ..	1	0	1
<i>C. albicans</i> ..	2	2	0

covery rate was 65%, 75% of the Gram-positive infections and 60% of the Gram-negative infections resolved completely. Both patients with *C. albicans* septicaemia died but in one the treatment response could not be evaluated because no specific anti-fungal treatment was given, the diagnosis being made after death. The outcome of the various septicaemias according to organism is shown in table IV. Two Gram-positive septicaemias are omitted because the outcome was obscured by the rapid development of a candida septicaemia.

One factor emerged which had possible value as a prognostic indicator for the outcome of the septicaemia: the underlying state of the bone marrow at the time of the septicaemia. The patients with acute leukaemia were graded for marrow state as follows: (1) newly diagnosed active disease, (2) drug-induced hypoplasia, (3) partial remission, (4) complete remission, and (5) drug-resistant relapse. In fact, it was often difficult to decide whether a leukaemic marrow was still in the initial active state or becoming hypoplastic due to chemotherapy at the time at which septicaemia developed. These two states were sometimes grouped together. The outcome of the septicaemia in relation to marrow state is shown in table V. The striking feature is the difference in outcome between those patients who contracted septicaemia on presentation or when they were hypoplastic due to chemotherapy—nine of 12 recovered, two of the

TABLE V—Outcome in relation to marrow State in 19 Patients with Acute Leukaemia

Marrow State	Total	No. Recovering	No. Dying
Newly diagnosed active leukaemia ..	3	3	0
Drug-induced marrow hypoplasia ..	5	3	2
Newly-diagnosed leukaemia/drug-induced hypoplasia ..	4	3	1
Partial or complete remission ..	0	0	0
Drug-resistant leukaemia ..	7	3	4

three deaths being due to candida septicaemia—and those who developed septicaemia late in the course of their disease when their leukaemia was drug-resistant—of these seven patients four died. The marrow state of the patients with aplastic anaemia was graded simply as mild aplasia or severe aplasia. In both episodes of septicaemia associated with the mild aplasia recovery occurred; in three of the four episodes of septicaemia with severe aplasia the patients died.

These differences are again emphasized when the 12 *E. coli* septicaemias are analysed in relation to marrow state and neutrophil count (table VI). Of the 12 patients with *E. coli* septicaemia five died and seven recovered. The neutrophil count was about 100/mm³ or less in every case except one. Of the five patients who died three had leukaemia in drug-resistant relapse and two had severe aplastic anaemia. Of the seven who recovered six had newly diagnosed leukaemia or drug-induced marrow hypoplasia; only one had drug-resistant leukaemia. A neutrophil count of 100/mm³ or less at diagnosis thus seemed to be relatively unimportant, in the *E. coli* septicaemias at least. Nevertheless, the effect of even a small rise in the neutrophil count during the course of treatment was appreciable (table

TABLE VI—Outcome in relation to Marrow State and Neutrophil Count in the *E. Coli* Septicaemias

Fatal <i>E. coli</i> Septicaemias (n = 5)		Non-fatal <i>E. coli</i> Septicaemias (n = 7)	
Marrow State	Neutrophils/mm ³	Marrow State	Neutrophils/mm ³
Drug resistant leukaemia	≤ 100	Newly diagnosed leukaemia	790
Drug-resistant leukaemia	≤ 100	Newly diagnosed leukaemia/D.I.M.H.	≤ 100
Drug-resistant leukaemia	≤ 100	Newly diagnosed leukaemia/D.I.M.H.	≤ 100
Drug-resistant leukaemia	≤ 100	Newly diagnosed leukaemia/D.I.M.H.	≤ 100
Severe aplastic anaemia	≤ 100	D.I.M.H.	≤ 100
Severe aplastic anaemia	≤ 100	D.I.M.H.	≤ 100
Severe aplastic anaemia	≤ 100	Drug-resistant leukaemia	115

D.I.M.H. = Drug-induced marrow hypoplasia.

TABLE VII—Neutrophil Count at Time of Recovery or Death in 17 Cases of Bacterial Septicaemia evaluable for Treatment Response in which Count was ≤ 120/mm³ at Time of positive Blood Cultures

Neutrophil Count/mm ³ at Time of Recovery or Death	No. of Complete Recoveries	No. of Deaths or Non-responders
More than 100	7	0
100 or less	2	8

VII). In 17 out of the 18 bacterial cases of septicaemia evaluable for treatment response in which the neutrophil count was 100/mm³ or less at the time of diagnosis the white cell count at that time of recovery or death was known. In seven out of nine patients who recovered the neutrophil count had risen to more than 100/mm³ at the time recovery was judged to have occurred. Five of these seven patients with more than 100 neutrophils/mm³ on recovery had “prognostically good” marrow states (newly diagnosed active leukaemia or drug-induced marrow hypoplasia) and two had “prognostically bad” marrow states (severe aplastic anaemia). There was no rise in the neutrophil count above 100/mm³ in any of the seven patients in whom no response occurred. All had “prognostically bad” marrow states (drug-resistant leukaemia and severe aplastic anaemia) except one, who was a newly diagnosed case of leukaemia.

The in-vitro sensitivities to gentamicin, cephalothin, colistin, and carbenicillin of the organisms of the 27 bacterial septicaemias are shown in table VIII. Gentamicin was the single most useful antibiotic, effective in all cases except one of the

TABLE VIII—In-vitro Antibiotic Sensitivities of Infecting Bacteria (2972)

Organism	No. of Cases	Proportion sensitive to:			
		Gentamicin	Cephalosporins	Carbenicillin	Colistin
<i>E. coli</i> ..	12	100%	100%	55%	100%
<i>Ps. aeruginosa</i> ..	2	100%	0	100%	100%
<i>Klebsiella</i> sp. ..	1	100%	100%	100%	100%
<i>Ent. cloacae</i> ..	1	100%	0	100%	100%
<i>Staph. aureus</i> ..	4	100%	100%	—	—
<i>Beta-haemolytic streptococcus</i> ..	2	0	100%	—	—
<i>Str. viridans</i> ..	3	66%	100%	—	—
<i>Staph. albus</i> ..	1	100%	100%	—	—
<i>B. subtilis</i> ..	1	—	—	—	—

three cases of *Str. viridans* septicaemia and both cases of beta-haemolytic streptococcal septicaemia. Colistin was equally effective in the Gram-negative cases but carbenicillin was effective against only half of the *E. coli* organisms isolated. The cephalosporins, of course, had no effect on the pseudomonal

infections or in the single case due to *Ent. cloacae*. The cephalosporins were universally effective in the Gram-positive infections, being more useful in such cases than gentamicin. No single penicillin covered all the Gram-positive infections; only cephalothin and cephaloridine did this.

Discussion

The main prognostic factor for the outcome of the septicaemia was the underlying marrow state. Drug-resistant leukaemia and severe aplastic anaemia were associated with a poor outcome, whereas newly diagnosed active leukaemia, leukaemia with drug-induced marrow hypoplasia, and mild aplastic anaemia were associated with a favourable outcome. Of course, in the former group of patients the contribution of infection to death is difficult to assess accurately as other factors such as bleeding are almost invariably present. It is important to remember the difference between the two groups of patients, however, when assessing the effectiveness of any given antibiotic regimen.

As shown by others²⁻³ neutropenia was important. As Whitecar *et al.*⁴ also found, recovery from septicaemia usually occurred in association with a rise in the neutrophil count, though in a few cases it seemed that measurable blood neutrophils were unnecessary for recovery. The same is true in our experience for severe lobar pneumonia; the mechanism by which considerable consolidation resolves without measurable neutrophils is a subject for conjecture.

The distribution of organisms among the 27 bacterial septicaemias is interesting for two reasons. Firstly, 40% of the infections were caused by Gram-positive organisms, and thus any "blind" antibiotic or combination of antibiotics must adequately cover Gram-positive as well as Gram-negative organisms. A cephalosporin is probably the best choice to cover these Gram-positive infections, with gentamicin a good second choice. A penicillin, of course, would have been preferable in several specific instances. It should be emphasized that though both examples of beta-haemolytic streptococcus in this series were resistant to gentamicin this is not always the case. The second feature of note was the relative paucity of pseudomonal infections in 1972. This is in sharp contrast to the experience of this unit in the previous year and to the experience of others;⁵ however, this fluctuation in pseudomonal predominance is not confined to this hospital. Other workers have noted a similar change in pattern.⁶

Until the 1972 trend was noted it was felt mandatory to include carbenicillin in any empirical antibiotic combination; at the end of 1972, however, in view of the low proportion of pseudomonal infections (7% of bacterial septicaemias in 1972) it seemed unjustifiable to include carbenicillin routinely, particularly since it is relatively damaging to veins and is expensive. In addition carbenicillin was effective against only half of the *E. coli* cultures, whereas the cephalosporins and colistin, as well as gentamicin, were effective against them all.

Gentamicin and colistin were the two most effective agents against the Gram-negative organisms, but colistin has no effect on Gram-positive bacteria. The combination of gentamicin and

a cephalosporin would have covered all the organisms cultured though, in fact, gentamicin alone would have covered them all except three of the Gram-positive infections. There is a growing body of evidence, however, that cephalothin can cause renal damage;⁷⁻¹² in particular, it was felt by Bobrow *et al.*,¹³ in a case of acute tubular necrosis, that the combination of gentamicin and cephalothin caused the nephrotoxicity rather than either agent alone. This suggestion was supported by a report by Optiz¹⁴ of nephrotoxicity in 14 patients receiving the combination. It also appears to increase the nephrotoxic potential of colistin.¹⁵ Until further information is available we think that it is unwise to use this potentially very valuable pair of antibiotics together unless circumstances demand it.

When the 1972 trend was noted we decided to use gentamicin alone initially, as this seemed safer than an all-encompassing multiple-drug regimen.⁵ We also felt that our previous results justified it. This practice had been operating for only three months, however, when the incidence of pseudomonal infections again rose sharply, and we felt it mandatory to include carbenicillin in our empirical antibiotic regimen in spite of in-vivo¹⁶ and in-vitro¹⁷ evidence of the inactivation of gentamicin by carbenicillin. We have therefore reverted to our former practice of using gentamicin and carbenicillin together, though we now discontinue the carbenicillin after four days if no pseudomonas is cultured and the patient is well. Our recent experience illustrates the fact that the bacterial flora of a given environment is a changing one. Because of toxicity to the patient, and regardless of financial considerations, it seems illogical to try to find an all-embracing multiple antibiotic regimen that is all things to all bacteria at all times in all places. If bacterial flora is changeable, then antibiotic regimens must remain flexible.

We should like to thank Dr. Beryl Jameson and the staff of the microbiology department, Sister S. Lynch and the nursing staff of the reverse barrier unit, and Dr. D. R. Gamble and the staff of the Public Health Laboratory, West Park Hospital, Epsom, for their help with the study, and Miss Jean Duncanson for her help with the manuscript.

References

- 1 Bodey, G. P., Buckley, M., Sathe, Y. S., and Freireich, E. J., *Annals of Internal Medicine*, 1966, **64**, 328.
- 2 Viola, M. V., *Journal of the American Medical Association*, 1967, **201**, 923.
- 3 Hughes, W., *American Journal of Diseases of Children*, 1971, **122**, 283.
- 4 Whitecar, J. P., Luna, M., and Bodey, G. P., *American Journal of the Medical Sciences*, 1970, **260**, 216.
- 5 Tattersall, M. H., Spiers, A. S. D., and Darrel, J. H., *Lancet*, 1972, **1**, 162.
- 6 Jameson, B., personal communication, 1973.
- 7 Rahal, J. J., Meyers, B. R., and Weinstein, L., *New England Journal of Medicine*, 1968, **279**, 1305.
- 8 Benner, E. J., *Antimicrobial Agents and Chemotherapy*, 1969, **9**, 417.
- 9 Thomas, B. L., *New England Journal of Medicine*, 1969, **280**, 505.
- 10 Pickering, M. J., Spooner, G. R., and Quesada, A. de, *Southern Medical Journal*, 1970, **63**, 426.
- 11 Simpson, I. J., *New Zealand Medical Journal*, 1971, **74**, 312.
- 12 Shapiro, R., and Kundarge, R., *Journal of Urology*, 1971, **106**, 823.
- 13 Bobrow, S. N., Jaffe, E., and Young, R. C., *Journal of the American Medical Association*, 1972, **222**, 1546.
- 14 Optiz, A., *et al.*, *Medizinische Welt*, 1971, **22**, 434.
- 15 Koch-Weser, J., *et al.*, *Annals of Internal Medicine*, 1970, **72**, 857.
- 16 McLaughlin, J. E., and Reeves, D. S., *Lancet*, 1971, **1**, 261.
- 17 Noone, P., and Pattison, J. R., *Lancet*, 1971, **2**, 575.