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OBSERVATIONS ON INDOL-POSITIVE *PROTEUS*

Gram-negative rods have assumed a major role in infectious disease, particularly among hospitalized patients. Among the *Enterobacteriaceae,* members of the genus *Proteus* may cause infections of the urinary[1] and respiratory[2] tracts, as well as meningitis,[3] soft tissue infections,[4] and septicemia.[5] However, mere isolation of these bacteria did not necessarily indicate the presence of infection. The most frequently encountered species has been the indol-negative *P. mirabilis* which has been studied from an epidemiological viewpoint, too.[7-9]

The three indol-positive *Proteus* (IPP) species, *P. morganii* (PMo), *P. vulgaris* (PV), and *P. rettgeri* (PR), are encountered far less often in clinical specimens. In 1967, we isolated a significant number of them, and the present study examines some factors of distribution, antimicrobial sensitivity, clinical significance, and transmission of these organisms.

MATERIALS AND METHODS

Selection of cultures

This retrospective study covers a nine-month period from January 1 until September 30, 1967. Only those patients in whom infection (but not necessarily at the site of later isolation) according to usual clinical criteria was suspected, had been cultured. Records of the Bacteriology Laboratory at the Yale-New Haven Hospital were reviewed for IPP isolations. Excluded from evaluation were (a) cultures from pediatric patients up to ten years of age, as these are processed in a different laboratory at this hospital, (b) cultures in which IPP were found in small numbers on the primary plates (less than 1+ growth as defined below, or less than 100,000 bacteria per ml. of urine) or in the enrichment broth only, (c) cultures from stools, as IPP may have been part of the normal flora.

Isolation and identification of IPP

Inoculation techniques were described in an earlier paper.[10] On urine plates inoculated with 0.001 ml., colony counts were performed; on plates from other specimens, a quantitative estimate of growth ranging from 1+ (little) to 4+ (abundant) was made. Non-lactose-fermenting colonies were picked from Desoxycholate Agar† plates and subjected to identification procedures described elsewhere.[11] IPP species were diagnosed according to test results published by the National Communicable Disease Center.[12] In the absence of phage typing or serotyping, different strains were arbi-

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trarily defined on the basis of different antimicrobial sensitivities and/or isolation from various wards at different times.

Antimicrobial sensitivity testing

This was done with a standardized single high potency disc method[13] using Sensi-Discs* of nine antimicrobials: kanamycin (30 μgm), nalidixic acid (30 μgm), chloramphenicol (30 μgm), streptomycin (10 μgm), tetracycline (30 μgm), ampicillin (10 μgm), cephalothin (30 μgm), colistimethate sodium (10 μgm), and nitrofurantoin (100 μgm).

Statistical evaluation

The t-test (Student) and the Fourfold Contingency Test[14] were used at the 1% level.

RESULTS

Freqency and distribution of IPP

Table 1 lists numerical data on patients, strains, and isolations. During the study period, the hospital counted six times as many outpatients as inpatients. However, IPP was isolated seven times more often from inpatients than from outpatients. On a percentage basis of hospital beds, inpatients with IPP isolations were distributed equally between medical and surgical services.

Of all IPP strains isolated, PMo were found 2.6 times as often as PR and 2.35 times as often as PV. There was an average of 15 strains per month, with a minimum of six in April and a maximum of 33 in July. The total patient count remained constant during the study period. *P. mirabilis*

TABLE 1. FREQUENCY OF IPP

		PMo	*PV*	*PR*	*Total*
Patients	in	63	28	24	115
	out	5	4	3	12
	total	68	32	27	127
Different strains		81	34	31	146
Isolations (one per site)		88	42	32	162

Abbreviations:

C, contributory
CA, community acquired
F, female
HA, hospital acquired
M, male
NC, not contributory
Oth, other
Pat, patients
PC, probably contributory
PMo, *Proteus morganii*
PR, *Proteus rettgeri*
PV, *Proteus vulgaris*
RT, respiratory tract
UT, urinary tract
Wd, wounds, pus, ear, eye

* BioQuest, Cockeysville, Md.

strains were isolated six times more frequently than all IPP strains together. Routine environmental cultures from operating, delivery, and emergency rooms were consistently negative for IPP. Wards were not checked.

Of all specimens received during the study period, 0.68% yielded IPP. Follow-up and repeat cultures had been left to hospital staff and were incomplete. Multiple isolations of the same strain from the same site were made in approximately 10% of the individuals affected, and the same strain was cultured from two or three different sites of the same individual in about 4%. There was no evidence of cross infections or of clustering of one strain on one ward.

Mixed vs. pure cultures

Table 2 demonstrates that over 80% of all strains were found together with other potential pathogens (over 50% with more than one). The species most frequently isolated with PMo and PV were *E. coli, Enterococci, Pseudomonas aeruginosa,* and *Klebsiella.* PR was isolated most commonly with *Pseudomonas aeruginosa* and *Enterococci.* Sixty-six per cent of all pure cultures came from urines.

Antimicrobial sensitivities

Table 3 lists the numbers of sensitive and intermediate (moderately sensitive) strains. Against all three species, kanamycin and nalidixic acid were the most effective drugs. At least half of the PMo and PV strains were sensitive to chloramphenicol, streptomycin, and tetracycline (with no inter-species difference), whereas less than 27% of the PR strains were sensitive to these drugs. The response of all species to ampicillin, cephalo-

TABLE 2. OCCURRENCE OF IPP WITH OTHER POTENTIAL PATHOGENS (Number of strains)

	PMo	*PV*	*PR*
Total strains	81	34	31
Pure or mixed with local normal flora	7	4	6
Mixed with potential pathogens	74	30	25
E. coli	40	10	6
Enterococci	33	7	11
Pseudomonas aeruginosa	27	5	10
Klebsiella	26	5	6
Proteus mirabilis	18	2	7
Staphylococci (coag. pos.)	13	5	4
Enterobacter	8	5	2
Others	27	8	17

TABLE 3. ANTIMICROBIAL SENSITIVITIES
(Number of sensitive and intermediate[18] strains)

Antimicrobial drug	*PMo*	*PV*	*PR*
Total strains	81	34	31
Kanamycin	76	33	31
Nalidixic Acid	76	31	24
Chloramphenicol	61	31	6
Streptomycin	53	25	8
Tetracycline	48	18	3
Ampicillin	8	4	5
Cephalothin	2	5	3
Colistimethate sodium*	2	2	4
Nitrofurantoin	54	8	0

* Colistin.

thin, and colistimethate sodium was equally poor. Nitrofurantoin affected about two thirds of the PMo and one quarter of the PV strains, but was ineffective against PR.

There was no difference in the sensitivities between strains isolated from different categories of patients (e.g., those on previous antimicrobial treatment *vs.* those on no such treatment; with hospital-acquired infections *vs.* community-acquired ones; with pure cultures *vs.* mixed ones). One-way cross-resistance was present in all species between kanamycin and nalidixic acid. Sensitivity "patterns" diagnostic for a particular species were not observed.

Site of isolation, sex, and age of patients

Table 4 relates these factors. During the study period, 66% of all in-

TABLE 4. RELATIONSHIP BETWEEN SITE OF ISOLATION OF IPP, AGE, AND SEX OF PATIENTS (Number of strains)

Species	*Age (years)*	*UT* M	*UT* F	*RT* M	*RT* F	*Wd* M	*Wd* F	*Blood* M	*Blood* F	*Oth* M	*Oth* F	*Total* M	*Total* F	*Percent of total*
PMo	11-50	3	2	1	0	6	7	0	0	1	1	11	10	25.9
	51-90	9	6	17	4	15	2	0	1	2	4	43	17	74.1
	Total	12	8	18	4	21	9	0	1	3	5	54	27	100.0
PV	11-50	0	3	0	0	3	4	0	0	0	0	3	7	29.4
	51-90	5	2	8	0	4	3	0	0	1	1	18	6	70.6
	Total	5	5	8	0	7	7	0	0	1	1	21	13	100.0
PR	11-50	3	0	0	0	2	1	0	0	0	0	5	1	19.3
	51-90	11	4	1	1	5	0	1	0	1	1	20	5	80.7
	Total	14	4	1	1	7	1	1	0	1	1	25	6	100.0

patients (with and without IPP) had been under 50 years of age, and the male:female ratio had been 1:1. The majority of patients with IPP, however, were over 50 and male. Strains isolated from different sites showed some pertinent features.

Urinary tract strains made up between 25% and 30% of the PMo and PV, but 58% of the PR strains. As would be expected in a population with urinary tract infections, the older age group was affected 3-4 times more frequently than the younger one. A clear predilection for males was seen in PR only.

Respiratory tract strains also comprised about 25% of the PMo and PV but only 6% of the PR strains. They were isolated from the sputa and in five instances from tracheal aspirates. They came almost exclusively from patients in the older age group. Here, PMo and PV showed a predilection for males.

Strains from wounds, pus, etc. They comprised approximately 40% of the PMo and PV strains and 25% of the PR strains. No age group predominated. Males were more often affected by PMo and PR than were females.

Strains from blood. They were isolated from two patients in their seventies.

Clinical conditions

Table 5 lists chronic clinical conditions of patients with IPP prior to the isolation of the organisms. It is apparent that most patients did have preexisting disease; only eight with PMo, two with PV, and one with PR seemed free of it. IPP was isolated particularly frequently following urinary tract instrumentation and following operations (PMo from wounds).

The acute illnesses presented clinically as urinary tract infection, pneumonitis (none primarily due to IPP), wound infection, and Gram-negative septicemia.

Pathogenic significance

Table 6 shows the relationship of IPP to infection at a specific site. Strains were called "contributory" if they were found in pure culture or if they predominated in mixed cultures from sites where infection was clinically present. They were called "probably contributory" if they occurred together in the same quantity with other pathogens at the site of clinical infection. If there was no evidence of an infection at the site of isolation, they were called "non-contributory." Overall, contributory, and probably contributory strains exceeded non-contributory ones by a factor of two or more in all species regardless of their origin from inpatients or outpatients. As expected, non-contributory strains were not found among the urinary

TABLE 5. PREEXISTING CLINICAL CONDITIONS (Number of patients)

	Isolation from								
	UT			*RT*			*Wd*		
	PMo	*PV*	*PR*	*PMo*	*PV*	*PR*	*PMo*	*PV*	*PR*
Total patients	20	10	18	22	8	2	26	14	7
Primary urinary tract disorder	9	4	12	3	1	0	8	1	1
Indwelling catheter or other previous urinary tract instrumentation	9	4	16	2	0	0	4	0	4
Chronic pulmonary disease	4	2	5	0	3	0	0	0	1
Previous respiratory tract instrumentation	1	1	1	6	4	1	1	0	0
Cardiovascular disease	4	2	7	8	6	0	6	4	1
Malignancy	5	2	5	4	2	0	7	3	4
Other major illness (non-infectious)	1	3	6	4	1	1	8	7	2
Postoperative state	5	3	8	10	2	0	18	6	1
Diabetes mellitus	1	2	3	4	1	0	3	3	0

tract isolates. On the other hand, they were encountered relatively frequently in sputa and wounds invaded with PMo. Almost all PR strains were contributory.

Community-acquired and hospital-acquired strains

Table 7 compares data on these strains. "Hospital-acquired" ones are defined as those that either could not be isolated from the patient at the

TABLE 6. RELATIONSHIP BETWEEN IPP ISOLATION AND DISEASE (Number of strains)

Species	*Designation*	*UT*	*RT*	*Wd*	*Oth*	*Total*
PMo	C	19	10	21	3	53
	PC	1	3	2	0	6
	NC	0	9	7	6	22
PV	C	7	6	8	0	21
	PC	3	1	4	0	8
	NC	0	1	2	2	5
PR	C	17	1	6	3	27
	PC	1	0	1	0	2
	NC	0	1	1	0	2

TABLE 7. COMMUNITY-ACQUIRED VS. HOSPITAL-ACQUIRED STRAINS

Species	Designation	Number of pat.	Sex		Age		Previous antimicrobials		Number of strains	Site of isolation				Contribution		
			M	F	11 to 50	51 to 90	+	—		UT	RT	Wd	Oth	C	PC	NC
PMo	CA	23	16	7	6	17	5	18	26	3	9	8	6	15	3	8
	HA	45	31	14	10	35	10	35	55	17	13	22	3	38	3	14
PV	CA	11	8	3	5	6	2	9	11	1	4	6	0	6	3	2
	HA	21	12	9	5	16	7	14	23	9	4	8	2	15	3	5
PR	CA	4	1	3	2	2	0	4	4	1	1	2	0	3	1	0
	HA	23	19	4	4	19	9	14	27	17	1	6	3	24	1	2

time of admission or were found only when clinical evidence of infection had become apparent after admission. "Community-acquired" strains were those isolated from patients who were clinically ill at the time of their first admission, or were in the process of becoming ill.

Overall, hospital-acquired strains were found two (PMo, PV) to six (PR) times more frequently than community-acquired ones; they prevailed by an even wider margin in urine specimens. Fifty per cent of them were isolated after local instrumentation (Foley catheterization, cystoscopy; bronchoscopy, intermittent positive pressure breathing) or operation. The percentage of contributory strains was slightly higher in the hospital-acquired group. The greater affinity for males and patients over 50 years, observed in both kinds of strains, reflects our patient statistics (Table 4). Surprisingly, patients on previous antimicrobial treatment (which had been largely effective against IPP strains) harbored IPP less frequently than those without previous treatment. This was a consistent finding irrespective of the origin of the strain from community or hospital. Thus, antimicrobial treatment was not a significant factor in the acquisition of a strain in the hospital.

Frequency of hospitalization

As Table 8 demonstrates, PR was the only species that was more often isolated on a patient's second or subsequent hospital stay than on his first one (other differences are not significant). Data on the relationship between hospitalization days and isolation of IPP could not be obtained with accuracy since not all cultures were taken at identical times during the patients' illnesses.

Death and IPP isolation

Of the 22 patients that died, 14 had harbored PMo, five, PV, and three, PR. Only one (with PV) had been under 50 years of age. All patients with PMo and PV and two with PR isolations who died succumbed to causes not attributable to IPP infection. One patient died from a PR septicemia secondary to pyelonephritis caused by the same organism.

TABLE 8. HOSPITALIZATIONS AND IPP ISOLATIONS
(Number of patients)

Hospital admission for underlying disease	*PMo*	*PV*	*PR*
First	28	11	6
Second or more	35	17	18
Outpatients	5	4	3

DISCUSSION

The retrospective character of this study accounts for several limitations which should be taken into consideration.

1. As in many studies of a similar nature, comparative data for the frequency of IPP and the incidence of preexisting conditions in the *entire* hospital population as well as in a non-hospitalized population of equal size are lacking.

2. The incidence of preexisting conditions, specifically of chronic urinary and respiratory tract disease, would be higher in any group consisting of patients over 50 years of age.

3. Estimates of hospital-acquisition of strains and of their contribution to disease are beclouded by subjective factors.[15,16]

4. Many patients were either not cultured at the time of their admission, or there was no record of earlier cultures from other hospitals. These factors have influenced the number of community-acquired strains. It was for this reason that an assessment of the rate of superinfections with IPP was not undertaken.

5. In about 96% of the patients with IPP isolation, only one site was cultured. This fact, as well as the factors mentioned in (1.) have probably influenced the number of non-contributory strains recorded. In particular, stool cultures were either not taken or not evaluated for IPP. This made it impossible to decide whether a strain was of exogenous or endogenous origin, since IPP species are known to occur in normal stools.[17] The absence of ward epidemics and the occurrence of community-acquired strains suggest an endogenous origin for at least a substantial proportion of our isolates.[4] However, other authors have observed exogenous IPP and *P. mirabilis* infections.[8,9,18,19] The organisms have been cultured from thermometers, bedpans, the air close to infected patients, and the hands of the hospital staff.[9,18]

In spite of these limitations, a number of pertinent facts can be deduced from our study.

PMo isolations occurred about 2½ times more frequently than PV and PR. It is well known that aside from the above mentioned factors, the frequency of isolation depends on the patient material of the hospital (age, chronicity of disease, length of hospitalization, incidence of cross infections). Our species ratio is, therefore, not directly comparable to that recorded by other authors.[15,18,20] The greater prevalence of *P. mirabilis* over the IPP, however, has been observed repeatedly.[1,4,6,15,20]

Antimicrobial sensitivity data for IPP also vary considerably, depending on the techniques used (MIC determinations, various diffusion tests with different interpretations).[8,15,21-23] Our results with kanamycin, nalidixic acid,

chloramphenicol, ampicillin, cephalothin, and colistimethate sodium are consistent, within the limitations of the disc method,[24] with previously reported MIC values.[21-26] As compared with strains from other laboratories, more of our PMo and PV strains were sensitive to tetracycline; also, more of our PV strains were sensitive to nitrofurantoin, while less were sensitive to streptomycin.[21,25,26] It is to be noted, however, that the term "strain" is rarely defined. Carbenicillin, which seems effective against a high percentage of IPP,[27] had not been available to us at the time of the study.

P. mirabilis strains are, on the whole, more sensitive than IPP to antimicrobials: resistance to tetracycline, polymyxin B, colistimethate sodium, and nitrofurantoin is most frequently observed,[21,26,28] whereas the other drugs listed in Table 3, as well as penicillin in high dosages, are effective against a high percentage of strains.

The lack of difference in sensitivity between hospital- and community-acquired strains has been observed in *P. mirabilis* causing urinary tract infection.[1] The degree of susceptibility, moreover, has been found independent of the site from which *Proteus* was cultured.[26] In these respects, the genus *Proteus* differs from the genera *Klebsiella* and *Enterobacter*.[16]

Certain host factors associated with other Gram-negative infections are apparently associated with IPP, too. In contrast to *P. mirabilis* strains,[1] IPP strains were more often hospital-acquired than community-acquired. About 80% of patients with IPP showed preexisting conditions (which certainly surpassed the frequency found in the entire hospital population). A similar figure was observed in the urinary tract infections with *P. mirabilis*.[7] A higher percentage was only seen in *Serratia* infections.[11] However, Diabetes mellitus, associated in one series in about 25% with urinary tract infection due to *Proteus*,[1] was not present in a significant number of the IPP patients. Also, only 22% (PMo) to 33% (PR) of the IPP patients had received previous antimicrobial treatment. This percentage is much lower than recorded in many other strains of Gram-negative rod infections,[11,16] and somewhat lower than that recorded for urinary tract infections with *P. mirabilis*. The importance of instrumentation, well documented for infections of the urine with *P. mirabilis*,[1] *Klebsiella*,[16] and *Serratia*,[11] is significant in our study as well.

As far as the interpretation of a strain as "contributory" is concerned, a particular problem arose with mixed cultures. We observed no case of pneumonia due to IPP alone (as described by others[2]). Cultures from the respiratory tract were mostly mixed with *Klebsiella, E. coli,* and *Pneumococci,* and these turned out to be of "primary clinical importance"[29] even though IPP may have predominated in the culture. Non-contributory strains most often replaced local normal flora.

There were inter-species differences between PMo and PV on one side and PR on the other. The latter and least frequent species isolated was most resistant to antimicrobials (while PMo and PV differed only in their susceptibility to nitrofurantoin), had a significantly higher preference for male patients, and also preferred those previously hospitalized. Urines were its most frequent source (a fact which would account for the higher percentage of contributory strains), and more strains were hospital-acquired than in the other species.

The virulence of IPP strains for animals is variable.[17] In our patients, highly virulent strains were probably rare: we saw only two cases of overwhelming infection, 20% of all strains were non-contributory, and among the 22 (19%) of our patients that died, only one succumbed to a cause (PR septicemia) that was immediately attributable to IPP.

SUMMARY

A retrospective study of 146 strains of indol-positive *Proteus* species isolated from adults is presented. The organisms, frequently resistant to many antimicrobial drugs, were most often isolated from mixed cultures, with a ratio of 2.6 (*P. morganii*) : 1.1 (*P. vulgaris*) : 1.0 (*P. rettgeri*). About 80% of the patients showed preexisting disease. Between 70% and 80% of the strains were found in patients over 50 years of age, were probably or certainly contributory to clinical illness, and were acquired in the hospital. The latter strains were particularly conspicuous in patients with previous instrumentation, but showed no association to previous antimicrobial treatment. In several respects, *P. rettgeri* differed from *P. morganii* and *P. vulgaris*.

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