THE INCIDENCE OF ANTIBIOTIC RESISTANCE IN GRAM-NEGATIVE BACILLI IN A GENERAL HOSPITAL

BY

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Five antibiotics—penicillin, streptomycin, aureomycin, chloromycetin, and terramycin—are now readily available for the treatment of diseases due to bacterial infection, and for the treatment of wounds infected either primarily or by hospital cross-infection. There is considerable overlapping in the selective activity of these antibiotics in that they are effective against Gram-positive bacteria in varying degree. The last four are also variably effective against the Gram-negative bacteria. There is, in addition, absolute selective activity in regard to some micro-organisms. Streptomycin alone is therapeutically effective against *Myco. tuberculosis*; chloromycetin has a special selective action against the *Rickettsiae*; aureomycin and terramycin have a special selective action against the larger viruses. It is, therefore, important in every case to attempt to obtain a pure culture of the infecting organism, and to evaluate its sensitivity to the various antibiotics.

The widespread use of antibiotics has also produced the problem of antibiotic resistant organisms, a problem which is as important, in relation to the Gram-negative bacilli, as it is to the Gram-positive cocci, and it was felt that an analysis of the results of routine sensitivity tests over 12 months might yield significant information.

Bact. coli, *P. vulgaris*, *Ps. pyocyanea*, *H. influenzae*, and *Bact. friedländeri* were studied with regard to their sensitivity to streptomycin, aureomycin, chloromycetin, and terramycin.

The period under review is the 12 months from January 1, 1950, to December 31, 1950. From January 1, 1950, to June 30, 1950, streptomycin only was available. From July 1, 1950, onwards aureomycin, chloromycetin, and terramycin were gradually added to the battery of antibiotics, until, in the final period, October 1, 1950, to December 31, 1950, all four antibiotics were used in the sensitivity tests.

The blood-agar plate medicated disc method of sensitivity testing has been used throughout. The method is simple and gives all the information that is required for control of antibiotic therapy. The antibiotics used in the tests were prepared in the following strengths.

Penicillin	...	...	...	500 units per ml.
Streptomycin	...	...	...	20 mg. per ml.
Aureomycin, chloromycetin, and terramycin	...	...	...	5 mg. per ml.

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One drop of the antibiotic was placed on the paper disc. A control organism was cultured on each plate.

Results

Bact. coli.—Three hundred and twenty-four strains have been tested with streptomycin, 177 strains with aureomycin, 168 strains with chloromycetin, 137 strains with terramycin.

The 12-month period has been subdivided into (1) January 1 to June 31, 1950 ; (2) July 1 to September 30, 1950 ; (3) October 1 to December 31, 1950. The results are shown in Table I.

TABLE I
SENSITIVITY TO STREPTOMYCIN, AUREOMYCIN, CHLOROMYCETIN, AND TERRAMYCIN OF STRAINS OF *Bact. coli*

Period of Isolation	Antibiotic	Total No. of Strains	Sensitive		Resistant	
			No.	%	No.	%
January 1 to June 30, 1950	Streptomycin only	115	61	53.1	54	46.9
July 1 to September 30, 1950	Streptomycin	87	45	51.7	42	48.3
	Aureomycin	65	45	69.2	20	30.8
	Chloromycetin	56	45	80.3	11	19.7
	Terramycin	25	19	76.0	6	24.0
October 1 to December 31, 1950	Streptomycin	122	64	52.4	58	47.6
	Aureomycin	112	43	38.3	69	61.7
	Chloromycetin	112	76	67.0	36	33.0
	Terramycin	112	73	65.0	39	35.0
July 1 to December 31, 1950	Streptomycin	209	109	52.1	100	47.9
	Aureomycin	177	88	49.7	89	50.3
	Chloromycetin	168	121	72.0	47	28.0
	Terramycin	137	92	67.1	45	32.9

The figures show that during these three periods the percentage of strains resistant to streptomycin has remained constant at 47–48%. This stabilization might be expected, as streptomycin had been in free use within the hospital for at least 15 months before the beginning of the period under review. Observations made on *Staph. pyogenes* over the same periods of time (Rountree, Barbour, and Thomson, 1951, and unpublished data) have shown that the percentage of streptomycin-resistant strains isolated in this hospital has now become stabilized around 25% to 30%. Although there is no direct evidence, such as is available for *Staph. pyogenes*, that streptomycin-resistant strains of *Bact. coli* have arisen in, and are characteristic of, hospitals, it is not unreasonable to suppose that such is the case.

There has been an increase in aureomycin-resistant strains in the three months ending December, 1950, from 30.8% to 61.7%. This increase is statistically significant ($\chi^2 = 13.098$; $P > 0.01$). A study of the values obtained in the next three-month period should show whether this increase is of a permanent nature. A similar trend may be occurring in relation to chloromycetin-resistant and terramycin-

resistant strains. This cannot, however, be established with any certainty until at least a further three-month period has been reviewed.

Another fact which emerges from the data is the high percentage of strains sensitive to chloromycetin (72%) and to terramycin (67.1%).

On analysing the figures for the period July to December, 1950, it was noted that 26 of 137 strains (19.4%) were completely resistant to all four antibiotics.

***P. vulgaris*.**—Two hundred and twenty-one strains have been tested with streptomycin, 77 with aureomycin and chloromycetin, and 72 with terramycin.

The 12-month period has been divided into (1) January 1 to June 30, 1950; (2) July 1 to December 31, 1950. The results are shown in Table II.

TABLE II
SENSITIVITY TO STREPTOMYCIN, AUREOMYCIN, CHLOROMYCETIN, AND TERRAMYCIN OF STRAINS OF *P. vulgaris*

Period of Isolation	Antibiotic	Total No. of Strains	Sensitive		Resistant	
			No.	%	No.	%
January 1 to June 30, 1950	Streptomycin only	70	61	87.1	9	12.9
July 1 to December 31, 1950	Streptomycin	151	113	74.8	38	25.2
	Aureomycin	77	6	7.8	71	92.2
	Chloromycetin	77	49	63.7	28	36.3
	Terramycin	72	11	15.2	61	84.8

The increase in streptomycin-resistant strains from 12.9% to 25.2% over these periods is barely significant ($\chi^2=4.17$; $P=0.15$); 63.7% of the strains were sensitive to chloromycetin, while only 7.8% were sensitive to aureomycin, and 11% to terramycin. It is obvious that in the treatment of infections with *P. vulgaris* streptomycin and chloromycetin are the antibiotics of choice.

***Ps. pyocyanea*.**—One hundred and thirty-one strains have been tested with streptomycin, 46 with aureomycin and chloromycetin, and 38 with terramycin.

The 12-month period has been divided into (1) January 1 to June 30, 1950; (2) July 1 to December 31, 1950. The results are shown in Table III.

TABLE III
SENSITIVITY TO STREPTOMYCIN, AUREOMYCIN, CHLOROMYCETIN, AND TERRAMYCIN OF STRAINS OF *Ps. pyocyanea*

Period of Isolation	Antibiotic	Total No. of Strains	Sensitive		Resistant	
			No.	%	No.	%
January 1 to June 30, 1950	Streptomycin only	68	34	50.0	34	50.0
July 1 to December 31, 1950	Streptomycin	63	26	41.3	37	58.7
	Aureomycin	46	3	6.5	43	93.5
	Chloromycetin	46	8	17.4	38	82.6
	Terramycin	38	18	47.4	20	52.6

The incidence of streptomycin-resistant strains (50–58%) has not altered significantly during the 12 months. The figures show clearly that this organism is very resistant to all antibiotic therapy, although response to terramycin may be expected in approximately 50% of cases. Aureomycin and chloromycetin would appear to be ineffective, since 80% to 90% of the strains tested were resistant to these substances.

Bact. friedländeri.—The figures shown in Table IV are for the whole period of 12 months. No percentages are given because the total number of strains investigated is too small. It should be noted, however, that the four strains investigated were all resistant to the action of terramycin, in contrast to the findings of Linsell and Fletcher (1950).

TABLE IV
SENSITIVITY TO STREPTOMYCIN, AUREOMYCIN, CHLOROMYCETIN, AND TERRAMYCIN OF STRAINS OF *Bact. friedländeri*

Period of Isolation	Antibiotic	Total No. of Strains	Sensitive	Resistant
January 1 to December 31, 1950	Streptomycin	35	32	3
	Aureomycin	4	3	1
	Chloromycetin	4	4	0
	Terramycin	4	0	4

H. influenzae.—The figures shown in Table V are for the whole period of 12 months, and again, because of the small numbers of strains investigated, no percentages are expressed.

TABLE V
SENSITIVITY TO STREPTOMYCIN, AUREOMYCIN, CHLOROMYCETIN, AND TERRAMYCIN OF STRAINS OF *H. influenzae*

Period of Isolation	Antibiotic	Total No. of Strains	Sensitive	Resistant
January 1 to December 31, 1950	Streptomycin	19	19	0
	Aureomycin	3	2	1
	Chloromycetin	3	3	0
	Terramycin	3	3	0

Streptomycin still appears to be the drug of choice for infections with *H. influenzae* and *Bact. friedländeri*.

Summary

Five micro-organisms—*Bact. coli*, *P. vulgaris*, *Ps. pyocyanea*, *H. influenzae*, and *Bact. friedländeri*—have been tested for sensitivity to streptomycin, aureomycin, chloromycetin, and terramycin.

The percentages of sensitive and resistant strains isolated over the 12-month period, January 1, 1950, to December 31, 1950, are given.

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Three hundred and twenty-four strains of *Bact. coli* were examined. The percentage of strains resistant to streptomycin has remained constant over the period at 47% to 48%. The percentage of strains resistant to aureomycin has increased from 30.8% to 61.7%. The increase is statistically significant ($\chi^2=13.098$; $P>0.01$). A similar trend may be occurring in relation to the chloromycetin and terramycin.

Two hundred and twenty-one strains of *P. vulgaris* were tested with streptomycin; 77 with aureomycin and chloromycetin, 72 with terramycin. There has been an increase in the streptomycin-resistant strains from 12.9% to 25.2% over the period. This is barely statistically significant ($\chi^2=4.17$; $P>0.15$). Of the strains tested with chloromycetin, 63.7% were sensitive. Streptomycin and chloromycetin are the antibiotics of choice in infections with *P. vulgaris*.

One hundred and thirty-one strains of *Ps. pyocyanea* have been tested with streptomycin; 46 with aureomycin and chloromycetin, 38 with terramycin. This organism is very resistant to all antibiotic therapy, but response to terramycin and streptomycin may be expected in approximately 50% of cases.

A small series of results with *Bact. friedländeri* and *H. influenzae* is shown. The four strains of *Bact. friedländeri* tested were all resistant to terramycin. Streptomycin still appears to be the antibiotic of choice for infections with these two organisms.

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REFERENCES

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ADDENDUM

Since this paper was written further tests have been carried out in the period January 1, 1951, to March 31, 1951, and the results are shown in Tables VI, VII, and VIII. During this period 514 strains of *Bact. coli*, 160 strains of *P. vulgaris*, and 83 strains of *Ps. pyocyanea* were tested. When the results are compared with those for the period July 1, 1950, to December 31, 1950, it will be seen that the

TABLE VI
SENSITIVITY TO STREPTOMYCIN, AUREOMYCIN, CHLOROMYCETIN, AND TERRAMYCIN OF STRAINS OF *Bact. coli*

Period of Isolation	Antibiotic	Total No. of Strains	Sensitive		Resistant	
			No.	%	No.	%
January 1 to March 31, 1951	Streptomycin	514	248	48.2	266	51.8
	Aureomycin	514	166	32.2	348	67.8
	Chloromycetin	514	300	58.4	214	41.6
	Terramycin	514	319	62.2	195	37.8

TABLE VII
SENSITIVITY TO STREPTOMYCIN, AUREOMYCIN, CHLOROMYCETIN, AND TERRAMYCIN OF
STRAINS OF *P. vulgaris*

Period of Isolation	Antibiotic	Total No. of Strains	Sensitive		Resistant	
			No.	%	No.	%
January 1 to March 31, 1951	Streptomycin	160	108	67.5	52	32.5
	Aureomycin	160	20	12.5	140	87.5
	Chloromycetin	160	101	63.1	59	36.9
	Terramycin	160	21	13.1	139	86.9

TABLE VIII
SENSITIVITY TO STREPTOMYCIN, AUREOMYCIN, CHLOROMYCETIN AND TERRAMYCIN OF
STRAINS OF *Ps. pyocyanea*

Period of Isolation	Antibiotic	Total No. of Strains	Sensitive		Resistant	
			No.	%	No.	%
January 1 to March 31, 1951	Streptomycin	83	39	47.0	44	53.0
	Aureomycin	83	6	7.2	77	92.8
	Chloromycetin	83	14	16.9	69	83.1
	Terramycin	83	24	29.0	59	71.0

trend is towards an increase in resistant strains, e.g. the strains of *Bact. coli* resistant to aureomycin have risen from 50.3% to 67.8% ; those resistant to chloromycetin have increased from 28.0% to 41.6% ; the strains of *Ps. pyocyanea* resistant to terramycin have increased from 52.6% to 71.0%.