THE EFFECT OF ANTIBIOTIC THERAPY ON THE EMERGENCE OF RESISTANT STAPHYLOCOCCI IN CUTANEOUS BACTERIAL INFECTIONS*

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The problem of infections due to antibiotic-resistant staphylococci is one of increasing concern to the medical profession. A large body of data on this subject has been accumulated and reported (1, 4, 6, 15) by clinicians and laboratory workers in all parts of the world. The vast majority of these studies refer to experience in hospitalized patients and the role of systemic antibiotic therapy as an important contributory factor to the increased incidence of such infections has been emphasized.

In this paper we are reporting our observations regarding the emergence of antibiotic-resistant *Staphylococcus aureus* following the topical treatment of cutaneous bacterial infections with various types of antibiotic ointments. Almost all of these patients who had local antibiotic therapy were observed in the outpatient department. As far as we know, except for sporadic cases which have been recorded (1), definite information (with bacterial cultures and antibiograms before and after local antibiotic treatment) regarding this facet of the antibiotic-resistant staphylococcus problem, is not available in the literature. In addition, we have included similar data for a smaller group of patients with cutaneous bacterial infections who were treated with antibiotics administered systemically.

It is not within the scope of this paper to review the literature on staphylococcal infections, but it does seem pertinent to summarize briefly those features of the problem with which all practicing physicians should be familiar.

Staphylococci are becoming the most important and most common cause of bacterial infections (2).

Staphylococcal infections resulting from cross-infections within hospitals may be the most serious current communicable disease problem (3).

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The percentage of strains of staphylococci resistant to antibiotics is related directly to the extent which the particular antibiotics are used (4, 5). However, there is very little evidence of increasing resistance to neomycin and bacitracin (5).

The percentage of antibiotic resistant strains of staphylococci is greater in hospitalized patients than in out-patients and the incidence of such strains is still lower in the general population (6, 7). The strains of staphylococci, isolated from physicians, nurses, and other hospital personnel in a given hospital, are often of the same phage types as those from the patients in that hospital, and a similar proportion of strains are antibiotic-resistant (6).

Severe, sometimes fatal, staphylococcal enteritis developing after prophylactic and therapeutic use of the broad spectrum antibiotics, has been reported (8).

There is evidence of an existing tendency for the increased occurrence of infections due to antibiotic-resistant strains of staphylococci in patients treated at home (6).

Antibiotic-resistant staphylococcal infections may occur among two or more members of families, and in some of these cases, infections may be traced by phage typing studies to one member of the family (especially infants) who acquired it in the hospital. In other instances, family infections may be independent of any hospital association (9).

Bacterial cultures and *in vitro* susceptibility tests are essential for the selection of the antibiotics to be used in the management of staphylococcal infections (5).

METHODS

Selection of Cases. A total of 354 patients were included in this study. They were selected on the basis of the following criteria: (1) Presence of an apparent clinical primary cutaneous infection, such as impetigo, furunculosis, etc., or a probable bacterial infection factor complicating contact dermatitis, atopic dermatitis or eczematous dermatitis of unknown etiology; (2) Isolation from involved sites, before therapy, of *Staph. aureus*

susceptible to the antibiotic which was administered systemically or applied topically; (3) Availability of follow-up cultures after varying periods of time following the antibiotic therapy.

Methods of Administration and Dosage. Topical antibiotic therapy either with tetracycline ointment, erythromycin ointment, neomycin ointment, bacitracin ointment, or combination neomycin-bacitracin ointment, was used in 245 cases. The only therapy for another 17 patients was the ointment base which was used in the preparation of the antibiotic ointments (control group). Systemic antibiotic therapy, either with tetracycline, erythromycin or novobiocin was used in 92 patients.

In almost all patients the dosage of tetracycline and erythromycin was 250 mgs. every six hours; in a few patients 500 mgs. every six hours was prescribed for the first 48 to 72 hours of therapy. The concentrations of the antibiotic ointments were as follows: 1% erythromycin, 1% tetracycline, 0.5% neomycin, 500 units bacitracin/gm, and a combination of 0.5% neomycin and 500 units bacitracin/gm. Usually the ointment base for the topical preparations was cholesterinized petrolatum, although in some patients the vehicle was a vanishing type base. A small percentage of the patients included in the tetracycline ointment group used a combination hydrocortisone-tetracycline preparation.

Laboratory Methods. Specimens for cultures were taken by using sterile saline-soaked cotton swabs. These were streaked on blood agar plates and incubated at 37°C for at least 48 hours. Cultures showing no growth at that time were discarded. Organisms were isolated and identified by conventional bacteriological methods. The classification used is that of *Bergey's Manual of Determinative Bacteriology*, Seventh Edition. Antibiotic susceptibility was tested by the disc method using Sensi-Discs (BBL). In addition, several hundred tests were done by the tube dilution technic. Investigative work (10) which has been done in our Department of Dermatology Research Laboratory, as well as the numerous reports of others (11, 12) show the two technics to be well correlated. In this study, we were interested primarily in the antibiotic susceptibility patterns (antibiograms) of *Staph. aureus* isolated before and after antibiotic treatment. We have divided these antibiograms into 9 groups (See Table III).

Bacterial susceptibility tests with tetracycline, neomycin, erythromycin, penicillin and novobiocin were done in all cases. Chloramphenicol, bacitracin, and streptomycin susceptibility tests were done in many cases but not for all of the organisms included in this study. Tests with streptomycin were done whenever the organism was resistant to tetracycline, erythromycin and penicillin; therefore, streptomycin was a part of the antibiogram only in groups VIII and IX (Table III). At present, chloramphenicol and streptomycin are included in our routine susceptibility tests for staphylococci, and the numerical designation of antibiograms proposed by one of us (13) is used.

RESULTS

In Tables I, II, III and IV, the results of the therapeutic trials, correlated with the cultures and antibiograms of *Staph. aureus* which were isolated before and after systemic and local antibiotic therapy, are summarized. There was a change from a susceptible to a resistant antibiogram in 17 of the 92 patients treated with systemic antibiotic therapy and in 16 of the 136 patients treated with either tetracycline ointment or erythromycin ointment. Of the 109 patients treated topically with neomycin, bacitracin, or the combination of neomycin-bacitracin, there was either no change in the antibiogram or *Staph. aureus* was not isolated following treatment. In addition there was no change in the antibiogram of *Staph. aureus* isolated before and after the use of the control ointment base in 17 patients.

Of the 11 patients from whom antibiotic-resistant staphylococci were cultured following systemic therapy with tetracycline, 8 were in-patients on the Dermatology Service and 3 were treated as out-patients; it is interesting that emergence of antibiotic-resistant organisms was observed in 8 of the 9 in-patients who were treated with tetracycline. Only 2 of 11 in-patients treated with erythromycin orally had this same sequence of events (Table IV).

Almost all of the patients who were treated with antibiotic ointments were out-patients. Our experience does not justify any conclusion regarding the relative incidence of emergence of antibiotic-resistant *Staph. aureus* following topical therapy for skin infections in patients who are treated in the hospital as compared with out-patients.

No difference in age or sex groups was found, nor did the type of cutaneous bacterial infection treated influence the tendency for development of antibiotic-resistant strains. The site of involvement did not appear to be a factor.

The change in antibiograms occurred within a period of seven days or less in 15 of the 33 pa-

TABLE I

Tabulation of cases

Antibiotic Resistant *Staph. Aureus* Cultured at Site of Cutaneous Infection after Systemic or Local Antibiotic Treatment

		Diagnosis	Antibiotic	Duration of Treatment*	Site of Involvement
1.	L. S.	Ecz. derm., imp.†	Tetracycline	IP‡—4 days	Extremities
2.	J. K.	Furuncle	Tetracycline	IP—11 days	Neck and arm
3.	M. K.	Ecz. derm., imp.	Tetracycline	OP§—5 days	Hands
4.	E. S.	Contact dermatitis, impetiginized	Tetracycline	IP—7 days	Hands
5.	J. L.	Ecz. derm., imp.	Tetracycline	IP—7 days	Arms, legs, hand
6.	R. S.	Ecz. derm., imp., with cellulitis	Tetracycline	IP—5 days	Feet
7.	H. A.	Ecz. derm., imp.	Tetracycline	OP—16 days	Arms and legs
8.	W. H.	Ecz. derm., imp.	Tetracycline	IP—16 days	Hands and feet
9.	S. B.	Ulcer, chronic	Tetracycline	IP—13 days	Leg
10.	A. G.	Ecz. derm., imp., with lymphangitis	Tetracycline	IP—4 days	Hands
11.	W. N.	Ecz. derm., imp.	Tetracycline	OP—2 days	Hands
12.	J. N.	Ecz. derm., "nummular" type	Erythromycin	OP—28 days	Extremities
13.	M. G.	Ecz. derm., imp.	Erythromycin	IP—3 days	Feet
14.	P. B.	Furunculosis	Erythromycin	OP—18 days	Multiple sites
15.	J. K.	Furuncle	Erythromycin	IP—23 days	Neck and arm
16.	A. K.	Ecz. derm., imp.	Erythromycin	OP—6 days	Hands
17.	L. C.	Furuncle	Novobiocin	IP—7 days	Upper lip
18.	T. C.	Impetigo and Paronychia	Tetracycline ointment	OP—16 days	Feet
19.	J. C.	Ecz. derm., imp.	Tetracycline-Hydrocortisone ointment	OP—15 days	Foot
20.	S. H.	Ecz. derm., imp.	Tetracycline ointment	OP—7 days	Hands
21.	R. B.	Ecz. derm., imp.	Tetracycline ointment	OP—23 days	Hands and feet
22.	G. B.	Dyshidrotic eruption	Tetracycline ointment	OP—9 days	Hands
23.	F. A.	Atopic dermatitis, impetiginized	Tetracycline-Hydrocortisone ointment	OP—14 days	Hands
24.	P. L.	Atopic dermatitis, impetiginized	Tetracycline-Hydrocortisone ointment	OP—19 days	Face, extremities
25.	A. K.	Ecz. derm., imp.	Tetracycline ointment	IP—8 days OP—4 days	Hands
26.	R. R.	Ecz. derm., imp.	Tetracycline ointment	OP—9 days	Ankle
27.	E. W.	Ecz. derm., imp.	Tetracycline ointment	OP—14 days	Feet
28.	M. F.	Ecz. derm., ankles	Tetracycline ointment	OP—17 days	Legs
29.	M. S.	Otitis externa	Tetracycline cream	OP—5 days	External auditory canal
30.	C. J.	Tinea pedis, impetiginized	Terramycin-Polymyxin-B ointment	OP—14 days	Feet
31.	C. L.	Ecz. derm., imp.	Erythromycin ointment	OP—27 days	Hands and feet
32.	B. T.	Ecz. derm., imp.	Erythromycin ointment	OP—7 days	Hands
33.	W. N.	Ulcers, leg, probably factitial	Erythromycin ointment	IP—4 days	Leg

* Duration of treatment refers to the number of days between culture done at time of initiation of therapy and the first culture showing emergence of antibiotic resistant *Staph. aureus.*

† Abbreviation for Eczematous dermatitis, impetiginized.

‡ In-patient.

§ Out-patient.

TABLE II

Summary of results regarding emergence of resistant Staph. aureus following oral and topical antibiotic therapy

	Total Cases	No. Resistant
Tetracycline (oral)	40	11
Erythromycin (oral)	49	5
Novobiocin (oral)	3	1
Tetracycline ointment	117*	13†
Erythromycin ointment	19	3
Neomycin-Bacitracin ointment	69	0
Neomycin ointment or lotion	26	0
Bacitracin ointment	14	0
Control ointment base	17	0
Total	354	33

* Includes 2 patients on Oxytetracycline ointment.

† Includes 1 patient on Oxytetracycline ointment.

tients; there might have been more patients in this group if cultures had been done more frequently.

In 10 of these 33 patients, therapeutic response was quite satisfactory in that essentially the bacterial infection component of the dermatitis had disappeared or was minimal at the time that the antibiotic-resistant staphylococcus was isolated. In this regard, it seems significant that in 7 of these 10 patients with a favorable response, both *Streptococcus pyogenes* and *Staph. aureus* were isolated prior to treatment.

In 17 patients of this group, the infection did not appear to improve significantly following antibiotic therapy; *Strep. pyogenes* and *Staph. aureus* were cultured before treatment in only 3 of these 17 patients.

In 6 of the 33 patients, the emergence of the antibiotic-resistant staphylococci was accompanied by an adverse effect on the course of the infection. In these cases, the patient's infection either improved initially, and then there was a significant relapse, or new suppurative lesions developed during the course of treatment. This sequence of events was illustrated dramatically in Case No. 23, in that the use of tetracycline ointment was followed by very rapid improvement of a severe impetiginized eczematous dermatitis of the hands. The relatively severe bacterial infection complicating this patient's dermatitis cleared completely within a period of 8 days, but this was followed by a very definite relapse of the infection at the same time that *Staph. aureus*, resistant to tetracycline, was cultured. Following this, there was another period of marked improvement of the infection when other antibiotic therapy was prescribed.

The results of bacterial cultures subsequent to the completion of antibiotic therapy were available for 17 of the 33 patients. In 8 cases, *Staph. aureus* with the same resistant antibiogram was cultured after periods of time varying from one month to 9 months. In 6 other patients, *Staph. aureus*, which was cultured weeks or months later, was not resistant (antibiogram Group I or II). In 3 patients, *Staph. aureus* was not cultured during periods of time varying from 10 days to one month, despite the previous isolation of antibiotic resistant staphylococci at the end of therapy. No such data are available for the other 16 patients.

In Table III, the antibiograms of the staphylococci which were isolated from the antibiotic resistant cases before and after treatment are tabulated. Before therapy, 26 of the 33 strains of *Staph. aureus* were either susceptible to all antibiotics tested or resistant only to penicillin (8 cases). After treatment periods varying from 2 days to 28 days, 30 of 33 strains were resistant to penicillin, and 27 were resistant to one or more broad spectrum antibiotics as well as to penicillin; 9 strains were resistant to erythromycin, tetracycline and penicillin.

COMMENT

As Barber and Burston (1) have emphasized, the mode or origin of antibiotic staphylococci is a complex subject. For example, some strains of staphylococci produce penicillinase which inactivates penicillin. Such a mechanism has not been recognized for other antibiotics. One explanation for the emergence of resistant bacteria is that there exists in a population of antibiotic-susceptible staphylococci a few organisms which are naturally resistant and during antibiotic therapy there is destruction or inhibition of the susceptible bacteria with survival of a few resistant ones. This permits a replacement of the susceptible by the resistant organisms resulting in the emergence of an antibiotic-resistant strain of staphylococci.

The emergence of antibiotic-resistant staphylococci in 17 of our 89 patients with cutaneous

TABLE III

Antibiograms of Staph. aureus

Isolated Before and After Treatment

Case No.	Antibiogram Before ℞	Antibiogram After ℞	Case No.	Antibiogram Before ℞	Antibiogram After ℞
1	Group VII	Group VIII	18	Group II	Group VI
2	Group II	Group VI	19	Group II	Group VI
3	Group IV	Group VI	20	Group I	Group VI
4	Group I	Group VI	21	Group I	Group III
5	Group I	Group VI	22	Group I	Group VI
6	Group I	Group VI	23	Group I	Group VIII
7	Group I	Group VI	24	Group I	Group VI
8	Group I	Group III	25	Group I	Group VI
9	Group II	Group VI	26	Group I	Group VI
10	Group II	Group VI	27	Group I	Group VI
11	Group II	Group VI	28	Group I	Group VIII
12	Group II	Group IX	29	Group I	Group III
13	Group I	Group VIII	30	Group I	Group VI
14	Group VI	Group VIII	31	Group VI	Group VIII
15	Group VI	Group VIII	32	Group II	Group IV
16	Group VI	Group VIII	33	Group I	Group VIII
17	Group VI	Group V			

All strains were susceptible to neomycin and all except two were susceptible to novobiocin.

Group I Susceptible to T, E and P
Group II Susceptible to T and E; resistant to P
Group III Susceptible to E and P; resistant to T
Group IV Susceptible to T and P; resistant to E
Group V Susceptible to T, E and P; resistant to N
Group VI Susceptible to E; resistant to T and P
Group VII Susceptible to T; resistant to E and P
Group VIII Resistant to T, E, P and S
Group IX Resistant to T, E, P, S and N

(T, E, P, S and N are abbreviations for Tetracycline, Erythromycin, Penicillin, Streptomycin and Novobiocin.)

bacterial infections who were treated with either tetracycline, erythromycin, or novobiocin systemically is not surprising. A possible explanation for the difference in results following the administration of these antibiotics is that in our hospital, erythromycin has been used less frequently than tetracycline and a much higher percentage of *Staph. aureus* is resistant to tetracycline than to erythromycin. In studies, which primarily have involved patients in hospitals, many investigators have emphasized the direct correlation between the increased use of antibiotics systemically and an increase in incidence of antibiotic-resistant strains of staphylococci.

We have not found similar data in the literature regarding the effect of topical antibiotic therapy in emergence of antibiotic-resistant strains of staphylococci except for 4 patients with skin infections recorded by Barber and Burston (1). The primary diagnoses in these 4 patients were pemphigus, contact dermatitis, extensive exfoliative dermatitis and leg ulcer. The first three patients had been treated with chlortetracycline ointment, the fourth with streptomycin and chloramphenicol ointments. Cultures were not done before therapy, but staphylococci, resistant to penicillin, streptomycin, and the tetracylines and to these antibiotics plus chloramphenicol in the latter two cases, were isolated after the prolonged local antibiotic treatment noted above. These authors advised against the prolonged use of topical antibiotic preparations, except for neomycin, which they consider probably the most suitable agent for the local treatment of staphylococcal lesions.

It is significant that in our series of 109 patients, the emergence of antibiotic-resistant *Staph. aureus* was not noted in a single case following

TABLE IV

Number of patients treated in hospital and as outpatients

	In-Patients	Out-Patients	Total Cases
Tetracycline (oral)	9 (8)*	31 (3)	40
Erythromycin (oral)	11 (2)	38 (3)	49
Novobiocin (oral)	2 (1)	1 (0)	3
Tetracycline ointment	4 (1)	113 (12)	117
Erythromycin ointment	4 (1)	15 (2)	19
Neomycin-Bacitracin ointment	2 (0)	67 (0)	69
Neomycin ointment or lotion	4 (0)	22 (0)	26
Bacitracin ointment	0	14 (0)	14
Control ointment base	1 (0)	16 (0)	17
Total	37	317	354

* Number of patients in whom there was emergence of antibiotic resistant *Staph. aureus* in parenthesis.

treatment with neomycin ointment, bacitracin ointment, or the combination neomycin-bacitracin ointment. Neomycin is an effective therapeutic agent for the topical treatment of cutaneous staphylococcal infections. However, it has been our experience that neomycin is not as effective as tetracycline in the local treatment of cutaneous bacterial infections if, on culture, *Strep. pyogenes* is either the only isolate or a part of the flora. Another factor which we consider important in regard to the use of topical preparations containing neomycin is that in recent years there has been a tendency for a small increase in the number of sensitization reactions to this antibiotic. It has been our experience that this undesirable sequence of events is more apt to occur in persons who have atopic dermatitis, or chronic eczematous dermatitis of the hands, feet, external auditory canal, and intertriginous areas. Prolonged topical application of neomycin, especially in patients with chronic dermatitis of any type, increases the probability of such sensitization reactions. It is for this reason that we do not use neomycin routinely in combination with hydrocortisone when topical steroid therapy is indicated. We believe that in general, if bacterial infection is a significant factor and if topical neomycin therapy is effective for the patient in question, a favorable therapeutic result will occur within a period of 7 to 14 days. If there is only questionable improvement, discontinuing the neomycin is in order. (This comment also applies in the use of other topical antibiotic preparations.)

Very few deaths due to staphylococcal septicemia complicating cutaneous bacterial infections have been recorded in the literature. Of 7 deaths due to systemic staphylococcal infections reported by Martin and his co-workers (14), one was due to a skin infection complicating dermatitis herpetiformis. During a period of three and one half months, Wysham and Kirby (3) accumulated a series of 189 hospitalized patients with staphylococcal infections; 100 of these infections appeared during the period of hospitalization and in 32 additional patients, the infection had its onset within 60 days after discharge from the hospital. They reported 24 deaths; one of these patients who succumbed was an apparently healthy forty-year-old male who had furunculosis complicated by "micrococcal" septicemia and in 2 other patients, staphylococcal infection of third degree burns was considered to be a major contributory factor.

CONCLUSIONS

Our present policy regarding the use of systemic and topical antibiotic therapy in the treatment of cutaneous bacterial infections may be summarized as follows:

Antibiotic therapy, both systemic and topical is prescribed in a discriminate manner. An effort is made to treat the patient specifically; the decision regarding the advisability of using antibiotic therapy in a given case, the selection of the antibiotic, and the route of administration (systemic or topical) are dictated by the cultural findings and the clinical situation.

The combination neomycin-bacitracin ointment* is preferred for the topical treatment of infections due to *Staph. aureus*. The addition of bacitracin increases the therapeutic effectiveness if *Strep. pyogenes* is isolated either in pure culture or as part of the bacterial flora. We avoid the prolonged use of topical preparations containing neomycin for patients who have secondarily infected atopic dermatitis, chronic eczematous dermatitis, or otitis externa.

If there is no significant improvement following the use of neomycin-bacitracin ointment for from 5 to 7 days, and if it appears that it is in order to

* Mycitracin ointment (Upjohn) was used for the patients included in this study.

continue topical antibiotic treatment, a trial of tetracycline ointment is instituted. It has been our experience that tetracycline ointment is more effective for cutaneous infections due to *Strep. pyogenes* than the neomycin-bacitracin combination ointment; therefore, under these circumstances, if topical therapy is indicated, usually tetracycline ointment is prescribed initially.

Discrimination in the use of antibiotics is essential, particularly in hospital practice. It must be assumed that the administration of antibiotics systemically to patients who are hospitalized with cutaneous bacterial infections will be followed by the colonization of the skin with antibiotic-resistant *Staph. aureus* in a relatively high percentage of cases. This is of obvious epidemiologic significance, and, in some patients, this sequence of events will influence the course of the patient's infection in an adverse manner. The use of strict isolation technics in caring for the in-patient with cutaneous bacterial infections will decrease the tendency for colonization of the skin lesions with the "hospital" strain of *Staph. aureus.*

Emergence of antibiotic-resistant *Staph. aureus* in skin lesions following either systemic or topical antibiotic therapy for cutaneous infections is less likely in out-patients than in in-patients. There is a need for more data regarding the epidemiologic significance of the emergence of antibiotic resistant *Staph. aureus* in the skin lesions of out-patients following the use of either systemic or topical antibiotic therapy for the treatment of cutaneous infections.

At the present time, except under unusual circumstances, we do not use erythromycin ointment or chloramphenicol ointment.

In treating both in-patients and out-patients with either systemic or topical antibiotic therapy, it is essential to repeat cultures and antibiograms if the course of the apparent bacterial infection is not satisfactory. Relapse or absence of progressive improvement following initial improvement, may be due to the emergence of antibiotic-resistant *Staph. aureus.*

SUMMARY

Our experience regarding the emergence of antibiotic-resistant *Staph. aureus* in skin lesions of patients with cutaneous bacterial infections, following therapeutic trials with tetracycline ointment, erythromycin ointment, neomycin ointment (or lotion), bacitracin ointment, or neomycin-bacitracin ointment, or after oral administration of tetracycline, erythromycin, or novobiocin is reported.

A total of 354 patients met the following criteria for inclusion in this study: 1) Presence of an apparent clinical primary or secondary cutaneous bacterial infection. 2) Isolation from involved sites, before therapy, of *Staph. aureus* susceptible to the antibiotic which was administered systemically or applied topically. 3) Availability of follow-up cultures after varying periods of time following the antibiotic therapy.

There was a change from a sensitive to a resistant antibiogram in 16 of 136 patients treated with either tetracycline or erythromycin ointment.

Of the 109 patients treated topically with either neomycin, bacitracin, or the combination of neomycin-bacitracin, there was either no change in the antibiogram or *Staph. aureus* was not isolated following treatment.

Emergence of antibiotic-resistant *Staph. aureus* was noted in 17 of 92 patients with skin infections, treated systemically with tetracycline, erythromycin or novobiocin.

The problem of emergence of antibiotic resistant *Staph. aureus* following the use of topical and systemic antibiotic therapy for the treatment of cutaneous bacterial infections is of greater significance in in-patients than in out-patients.

Our present policy regarding the use of systemic and topical antibiotic therapy for the treatment of bacterial infections of the skin is summarized.

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DISCUSSION

DR. J. WALTER WILSON (Los Angeles, Calif): Were the strains of staphylococci which were called resistant by the authors the bacteriophage types 52/81 or 42B—the notorious so-called hospital strains?

I also want some clarification as to just how a resistant strain emerges. This word emerge is very good—all it means is that you don't see it at first and sometime thereafter you do see it. I wonder whether or not, actually, the material which is put on the original sensitivity test cannot contain tiny quantities of resistant organisms as well as nonresistant ones to begin with, and perhaps the latter are killed by the drug, leaving the resistant ones. It is a little hard for me to believe that new mutations can always produce this 52/81 or some such species. I prefer to believe that these strains are now scattered all over the world and are simply being recovered in more and more of our specimens.

DR. PETER BEAL (Redwood City, Calif.): I would just like to ask if any attempt has been made to follow up the recovered cases with cultures of the nose and throat?

Many of our skin contaminants are bacteria in most instances—often from the nose and throat. I think it would be significant to know that once you have discovered an antibiotic-resistant organism on their skin—whether these individuals actually harbor them in their nose and throat and whether they might not be carriers that might contaminate others.

DR. NORMAN N. EPSTEIN (San Francisco, Calif.): Concerning the use of small doses of antibiotics internally over a long period of time, such as in the treatment of acne vulgaris, I would like to ask if Dr. Livingood believes there is any serious danger of the patient developing serious evidence of antibiotic resistant disease?

DR. THEODORE CORNBLEET (Chicago, Illinois): In those patients with resistant organisms who went on to recovery, was the therapy changed? If it was not, do you feel that the *in vitro* results are relevant to the clinical findings?

DR. STEPHEN ROTHMAN (Chicago, Ill.): I was very much impressed with what Dr. Livingood has shown us. It seems that infections of the skin may be cleared by antibiotics to which the organisms are resistant *in vitro*.

In my experience, too, *in vitro* testing of sensitivities has only limited clinical value. Nonconsistent therapeutic results are rather common.

DR. CLARENCE S. LIVINGOOD (in closing): I wish to thank the discussors for their comments and questions.

Dr. Wilson, the strains of *Staph. aureus* which were isolated in this series of patients were not phage typed. Our data regarding the emergence of antibiotic resistant *Staph. aureus* in the 33 patients following either topical or systemic antibiotic therapy refer only to a change in the antibiogram of the organism, which may or may not mean that different phage types of *Staph. aureus* were isolated before and after treatment.

Dr. Wilson's suggestion that there might have been a "killing off" of the sensitive organisms because of the possibility of carrying over a small amount of the antibiotic to the culture tube, is a valid one. However, I do not think that this sequence of events occurred in our cases. Topical

antibiotic therapy was discontinued for a period of approximately 12 hours before the follow-up cultures were done. In some of our patients included in this group, cultures were done one to several weeks after treatment was discontinued.

Our experience in regard to the emergence of antibiotic resistant *Staph. aureus* in the skin lesions of patients who were hospitalized with cutaneous bacterial infections and treated with systemic antibiotic therapy is not unique. However, as far as we know, this is the largest group of patients in whom emergence of antibiotic-resistant *Staph. aureus* has been observed following topical antibiotic therapy with either tetracycline ointment or erythromycin ointment. This sequence of events appears to occur in a larger percentage of cases than we had anticipated. We plan to evaluate the epidemiologic significance of this finding, and in these studies, phage typing of the strains of *Staph. aureus* will be essential. At the present time, it seems doubtful that the use of tetracycline ointment is resulting in a significant increase of antibiotic resistant strains of *Staph. aureus* in the general population. It is significant that the topical application of neomycin or bacitracin was not followed by the emergence of antibiotic resistant strains of *Staph. aureus* or at least not in our group of patients.

Dr. Norman Epstein has asked about the treatment of acne with broad spectrum antibiotics. Our data do not make it possible to answer his question but this is another problem which we are planning to investigate.

Dr. Rothman has asked a question regarding the clinical course of our patients in whom there was emergence of antibiotic-resistant *Staph. aureus* following antibiotic therapy. Also, he has stated that often there does not seem to be good correlation between the therapeutic results with antibiotics and *in vitro* sensitivity tests. In some of our patients, the emergence of an antibiotic resistant organism did not seem to have any effect on the clinical course of the infection, but in other cases, this sequence of events was accompanied either by failure to improve beyond a certain point or by relapse of the infection. This is covered in the paper in detail. It seems to me that the practical point to be considered, is that, in patients, who have bacterial infections due to *Staph. aureus*, it is essential to repeat the cultures and the antibiograms if the course of the infection is not proceeding in a favorable manner. The reason for this is that in some cases, failure to improve may be explained by the emergence of an antibiotic resistant strain of *Staph. aureus* and a change in therapy is indicated. It is not a simple matter to correlate the clinical course of a staphylococcal skin infection and the results of cultures and *in vitro* sensitivity tests. For one thing, the isolation of *Staph. aureus* does not mean necessarily that the presenting eruption is a bacterial infection either primary or dermatitis complicated by staphylococcal infection. Therefore, failure to improve with specific antibiotic therapy for a sensitive strain of *Staph. aureus* may not indicate poor correlation with the results of the sensitivity tests since factors other than the apparent infection may account for the failure to improve. Furthermore, the same reasoning may be used in attempting to explain improvement following antibiotic therapy for a skin lesion from which an antibiotic resistant strain is isolated because isolation of *Staph. aureus* may indicate colonization of the involved sites with no pathogenic effect.