The epidemiologist—like the pathologist—has convincing arguments to offer against the indiscriminate dosing with antibiotics for minor illnesses, diagnosed or undiagnosed. Revealed here are some of the end effects upon public health to be anticipated from the practice.

Observations on the Epidemiological Spread of Antibiotic-Resistant Staphylococci, with Measurements of the Changes in Sensitivity to Penicillin and Aureomycin*†

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STAPHYLOCOCCI which are not inhibited by the concentrations of penicillin achieved in the body fluids by customary methods of therapy, so-called penicillin-resistant staphylococci, have been obtained from hospitalized patients, from patients attending outpatient clinics, and from healthy subjects in the general population. It has been shown by various investigators that the percentage of penicillin-resistant strains recoverable from patients in hospitals has increased from year to year during the period in which penicillin has been available. The appearance of resistant strains has sometimes followed treatment with penicillin, but often, perhaps more often, has been due to the spread of resistant strains to hospitalized patients from other patients and from attendants. Since recent reports have indicated that 37–70 per cent of hospitalized patients carry penicillin-resistant staphylococci,[1-6] it has seemed important to us to determine what happens to these strains when the patient returns to his home.

Although aureomycin has been in general use for only three years, there is evidence that resistant strains of staphylococci are appearing in hospitalized patients.[3, 5, 7, 8] Information in regard to the presence of aureomycin-resistant strains in the general population is not available, although there are indications that infections caused by strains of staphylococci resistant to aureomycin are becoming more prevalent. In order to obtain more information on the circumstances under which antibiotic-resistant staphylococci spread from person to person, we have investigated the sensitivity to aureomycin as well as to penicillin of the strains of staphylococci present in the noses and

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throats of patients discharged from a contagious disease hospital and of their household contacts. The present paper is a report of these studies.

METHOD

Pharyngeal cultures were obtained by moistening a sterile applicator in tryptose-phosphate broth, swabbing both sides of the pharynx (and tonsils, if present) with the applicator and placing it in tryptose-phosphate broth for transmission to the laboratory. Nasal cultures were taken similarly by the use of one applicator for both nares. In the first part of the study, cultures were taken from the pharynx only. Later a culture was taken from both the nose and the pharnyx on each patient and family contact studied. In the laboratory, the applicator was streaked across an agar plate containing 2 per cent sheep blood. In the case of hospital personnel and inpatients, the plates were streaked within an hour of the time of swabbing. In the case of patients at home and their household contacts, this interval varied from one to four hours.

The presence and characteristics of the colonies of staphylococci on the blood agar plates were noted. A single colony was picked for study from each plate unless the colonial characteristics differed, in which case a specimen of each type of colony was subcultured.

Minimal inhibitory concentrations of penicillin and aureomycin * (and in some cases of streptomycin, terramycin, or chloramphenicol) or both, were performed by serial twofold dilutions in tubes of tryptose-phosphate broth. The lowest concentration showing absence of growth on inspection after 18 hours incubation was taken as the minimal inhibitory concentration (also referred to as the "sensitivity" of the strain to that particular antibiotic).

* The aureomycin used in this study was supplied by the Lederle Laboratories Division, American Cyanamid Company.

The coagulase test was done by the method of Fisk.[9] Hemolysis was determined from the blood-agar plate. Subcultures on plain tryptose-phosphate agar plates were used to observe pigment production.

Staphylococcus bacteriophages were obtained through the courtesy of Dr. G. B. Leyton of Winnepeg, Manitoba, Canada.

Routine nasopharyngeal cultures were taken on patients during hospitalization and at the time of discharge. Follow-up cultures were taken at intervals of approximately two weeks for at least eight weeks after the patient returned home, and in some instances for as long as 21 weeks. Cultures were also made from the noses and throats of hospital personnel, including physicians, nurses, and orderlies. A record was made of the occurrence of respiratory infections in the patients at home and the household contacts as well as therapy with antibiotics. All of the staphylococci obtained on culture have been included in the tabulations irrespective of their ability to produce pigment or hemolyze blood and regardless of whether they were coagulase positive or negative. A study of the occurrence and transmission of antibiotic-resistant strains among the patients during hospitalization will be reported elsewhere.[10]

RESULTS

Initial and adequate follow-up cultures were made on 54 patients who carried staphylococci in the nose or pharynx, or both, at some time during their hospital stay and on their 209 household contacts. Household contacts varied from one to nine and averaged 3.8 per patient. From Figure 1, it can be seen that 74 per cent of the cultures taken from the patients at the time of discharge from the hospital contained staphylococci. This percentage decreased irregularly during the weeks after the patients left the hospital. From

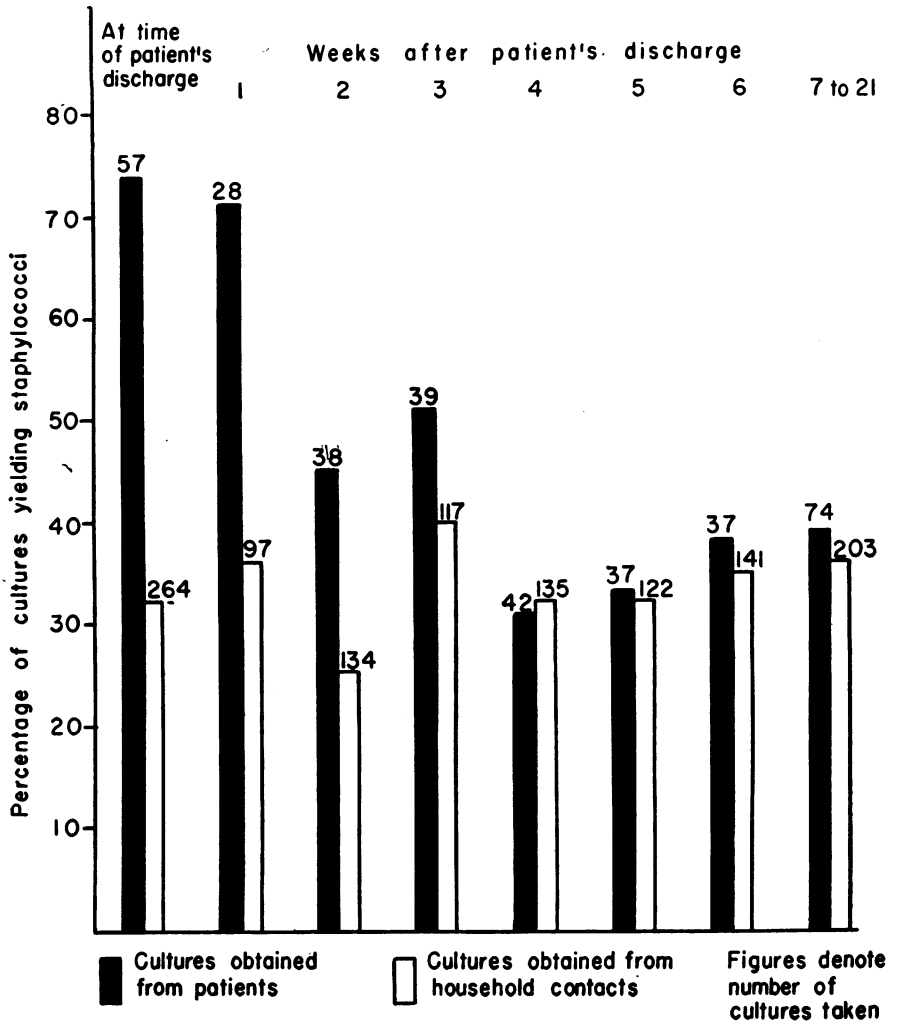

FIGURE 1—Percentage of nose and throat cultures from patients and family contacts which were positive for staphylococci

the fourth week on, it remained between 31 per cent and 39 per cent. On the other hand, in the case of household contacts, the percentage of cultures taken which contained staphylococci remained relatively constant, between 25 and 40 per cent. Altogether 1,213 cultures were taken from the noses or the throats of household contacts of which 404, or 33 per cent, were positive for staphylococci. From the fourth week after discharge, 191 cultures were taken from patients of which 69, or 36 per cent, were positive, and 601 cultures were taken from the contacts of which 204, or 34 per cent, were positive. From these data, it is apparent that staphylococci were present in the nose or throat of a larger proportion of patients for the first three weeks after discharge from the hospital and that after that period there was no significant dif-

TABLE 1

Concentrations of Penicillin Required To Inhibit Strains of Staphylococci Obtained from Noses and Throats of Patients and Household Contacts

Group Studied	Time at Which Cultures Were Taken	Number of Strains Studied	Percentage of Strains Requiring Various Concentrations of Penicillin to Inhibit Growth			
			<0.1 Unit/ml.	0.1–0.9 Unit/ml.	1.0–9.9 Unit/ml.	10 Unit/ml. and Over
Hospital Personnel	At intervals during study	47	9	6	34	51
Patients	At discharge from hospital	42	12	0	19	69
	Weeks after discharge:					
	1–2	37	11	13	13	63
	3–4	33	36	6	9	49
	5–6	27	56	4	7	33
	7–21	29	62	7	3	28
Household Contacts	At time of patient's discharge from hospital	84	65	3	2	30
	Weeks after discharge:					
	1–2	68	62	6	4	28
	3–4	89	67	5	10	18
	5–6	91	59	7	3	31
	7–21	74	71	4	5	19
	All times	406	65	5	5	25

ference in the number of patients and in the number of contacts from whom staphylococci were obtained.

Table 1 shows the percentage of strains of staphylococci recovered from the nose or throat which were inhibited by various concentrations of penicillin in relation to the time when the cultures were taken. At the time the patients were discharged from the hospital, 69 per cent of the staphylococci required for inhibition 10 units of penicillin per ml. or more and 88 per cent required for inhibition one unit or more of penicillin. The remaining 12 per cent were inhibited by less than one unit per ml. For purposes of comparison, the penicillin sensitivity of the staphylococci recovered from the noses and throats of the hospital personnel is shown. Fifty-one per cent of these strains required for inhibition 10 units or more per ml. of penicillin and 85 per cent, one unit or more. The percentage of resistant strains recovered from the patients in the study decreased progressively through the sixth week after the patient left the hospital (regardless of whether one unit or 10 units was taken as the criterion of resistance).

If all the strains cultured after the patient's fourth week at home were to be grouped together, the percentage inhibited by 10 units or more would be 30 per cent, and by one unit or more, 36 per cent. This should be compared with the sensitivity to penicillin of the staphylococci obtained from the household contacts. In this group the proportion of resistant strains remained essentially the same throughout the period of the study. If all of the strains were to be added together regardless of when they were obtained, the proportion requiring 10 units or more of penicillin per ml. for inhibition would be 25 per cent and the proportion requiring one unit or more per ml., 30 per cent. If only the strains isolated from the contacts after the patient's fourth week at home were to be included in the calculation, the percentages would be exactly the same, 25 per cent and 30 per cent, respectively. Accordingly, the propor-

tion of resistant staphylococci obtained from patients after the fourth week was only slightly higher than the proportion of resistant strains obtained from the contacts during that same period or during the entire period of the study.

Similar data for aureomycin sensitivity are shown in Table 2. At the time of the patient's discharge, 78 per cent of staphylococci required 10 μg. or more of aureomycin per ml. for inhibition. This may be compared with the 64 per cent of staphylococci obtained from hospital personnel which required the same concentrations of aureomycin per ml. for inhibition. The proportion of strains from patients which required these high concentrations for inhibition gradually fell until after the sixth week it reached 14 per cent. Among the household contacts, the proportion of strains which required 10 or more μg. per ml. for inhibition fluctuated between 2 per cent and 12 per cent. For the entire period of observation this proportion was 7 per cent.

The proportion of strains resistant to one or more μg per ml. of aureomycin followed the same pattern, although it was quantitatively different. At the time the patients left the hospital, 90 per cent of the strains required these concentrations of aureomycin for inhibition. The proportion dropped slightly but remained relatively stationary from the third week on, varying between 59 per cent and 70 per cent. The proportion of strains among household contacts which required one or more μg. per ml. of aureomycin for inhibition varied between 34 per cent and 66 per cent. If all the strains obtained from household contacts during the period of the study were to be grouped together, 51 per cent of them would be inhibited by this amount of aureomycin. It appears, therefore, that the proportion of patients' strains which were highly resistant to aureomycin dropped more slowly after the patient left the hospital than in the case of strains which were highly resistant to penicillin, but that eventually the proportion was slightly lower than in the case of penicillin. On

TABLE 2

Concentrations of Aureomycin Required To Inhibit Strains of Staphylococci Obtained from Noses and Throats of Patients and Household Contacts

Group Studied	Time at Which Cultures Were Made	Number of Strains Studied	Percentage of Strains Requiring Various Concentrations of Aureomycin to Inhibit Growth			
			<0.1 μg./ml.	0.1–0.9 μg./ml.	1.0–9.9 μg./ml.	10 μg./ml.
Hospital Personnel	At intervals during study	47	0	8	28	64
Patients	At discharge from hospital	42	0	10	12	78
	Weeks after discharge:					
	1–2	37	0	13	22	65
	3–4	33	0	36	28	36
	5–6	27	0	30	37	33
	7–21	29	0	41	45	14
Household Contacts	At time of patient's discharge from hospital	85	4	47	46	4
	Weeks after discharge:					
	1–2	68	3	63	24	10
	3–4	90	6	43	43	8
	5–6	88	0	34	64	2
	7–21	73	1	47	40	12
	All times	404	3	46	44	7

TABLE 3

Fate of Strains of Staphylococci in the Nose and Throat of Patients and Household Contacts

Fate of Strains of Staphylococci	*Number*	*Per cent*
Number of households investigated	54	100
Strain transferred from patient to contact	7	13
Strain transferred from contact to patient	10	19
Patient's and contact's strains grew independently without transfer	5	9
Cultures of patient's nose and throat became negative for staphylococci	24	44
Patient acquired strain unrelated to strains carried by household contacts	3	6
Fate of strains could not be determined	5	9

the other hand, the proportion of strains which were moderately resistant to aureomycin dropped only slightly and remained much higher than the proportion of strains which were moderately resistant to penicillin. Regardless of which criterion was used for the determination of resistance, the proportion of aureomycin-resistant strains in contacts was slightly lower than in the case of patients. It should be added that wherever determinations of sensitivity to terramycin and chloramphenicol were carried out, the changes in the sensitivities of the various strains of staphylococcus to these antibiotics were found to parallel the changes in sensitivity to aureomycin. There was no relationship among the sensitivities of the strains to aureomycin, streptomycin, and penicillin.

The fate of the individual strains of staphylococci which were present in the nose or throat, or both, of patients or contacts is shown in Table 3. This was determined by bacteriophage typing, when the strains could be typed by this method, and by the sensitivity of the strains to penicillin, aureomycin, and streptomycin when the results were sufficiently clear-cut so that there was no question as to whether the observed strain was the same or a different one. In five of the 54 families studied, a definitive answer could not be obtained by either of these methods. Among the remaining families, the strain carried home from the hospital by the patient was transferred to a member of the household in seven instances. A strain which was present in a household contact before the patient left the hospital was later transferred to the nose or throat of the patient in 10 instances. In the case of five families, the patient retained his strain and the contacts retained theirs without any transfer. In the largest number of cases, 24, or 44 per cent, of the families, the strain carried home by the patient could not be cultured at a later date and was not replaced by another strain of staphylococcus. In three families, the strain which the patient carried home from the hospital could not be cultured at a later date and was replaced by another strain of staphylococcus which was not cultured from other members of the family at any time. The number of contacts in the household bore no relation to the transfer or nontransfer of strains from patient to contacts, or vice versa.

Transfer of a strain from patient to household contact, or vice versa, occurred more frequently when the staphylococcus had its site of origin in the throat rather than in the nose. Among the patients and contacts on whom both nose and throat cultures were taken in every instance, staphylococci were cultured from the throat in 27 instances. In eight, 30 per cent, of these cases the strain was transferred either from patient to contact or from contact to patient. On the other hand, staphylococci were cultured from the nose in 57 instances, in six of which, 11 per cent, the strain was transferred. This difference in frequency of transmis-

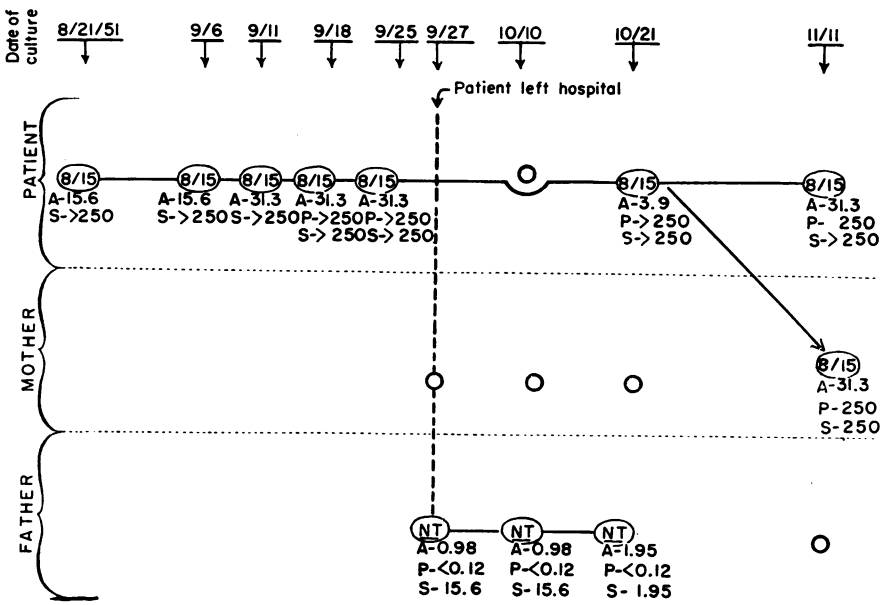

FIGURE 2—Spread of an antibiotic-resistant staphylococcus from patient to a family contact Numbers within circles indicate phage type. Types 8 and 15 correspond to Phage types 8406 and 8404 according to strains obtained from Dr. G. B. Leyton, director of laboratory services, Department of Health and Public Welfare, Winnipeg, Manitoba, Canada

NT = no phage type obtained
O = no staphylococci obtained on culture
A = number of micrograms of aureomycin per ml. required for inhibition of growth
S = number of micrograms of streptomycin per ml. required for inhibition of growth
P = number of units of penicillin per ml. required for inhibition of growth

sion has a 10 per cent probability of occurrence by chance, according to the chi square test.

Figure 2 shows the spread from a patient to a family contact of a staphylococcus which was resistant to aureomycin, penicillin, and streptomycin. Each of five throat cultures taken during hospitalization yielded strains of staphylococcus which were of the same phage type and which required for inhibition 15.6 to 31.3 μg. of aureomycin per ml., and were not inhibited by 250 units of penicillin or 250 μg. of streptomycin per ml. A staphylococcus could not be grown from the first culture of the patient's throat after discharge from the hospital but the previous strain reappeared on the second and third cultures. This last culture was taken eight weeks after the patient left the hospital. On that same day, staphylococci were cultured from the mother's throat for the first time since the day of the patient's discharge, and this organism was found to be identical with the one which had been repeatedly cultured from the patient's throat. A different strain of staphylococcus which could not be typed with the bacteriophage strains available was cultured several times from the father's pharynx.

DISCUSSION

Staphylococci which are resistant to antibiotics may be acquired under three different sets of circumstances:

1. The resistant strain may appear

while the patient is under treatment with the antibiotic in question or a closely related antibiotic.

2. The resistant strain may be acquired while the patient is in the hospital even though antibiotics are not being administered. (Presumably the resistant strains are transferred from other patients who have been given antibiotics either directly or, more often, by means of hospital personnel acting as carriers.)

3. The resistant strain may be acquired in the community from symptomless carriers.

If the spread of antibiotic-resistant strains of bacteria is to be controlled, the relative importance of these three mechanisms must be determined. The first two of these have been observed frequently. The third mechanism has not been investigated in detail, although it can be inferred from the fact that when samples of the general population have been studied, up to 18 per cent of the carriers have been found to harbor penicillin-resistant staphylococci.[10-13] The observations reported in this paper demonstrate that staphylococci which are resistant to penicillin and aureomycin occur in larger numbers among patients for several weeks after their discharge from the hospital than in members of the population at large. Transfer of strains of staphylococci to one or more of the household contacts was found to take place from the nose or throat of 13 per cent of the patients observed. A significant increase in the carrier rate of resistant strains was not observed, however, among household contacts after the arrival of patients in the households, nor among the patients subsequent to the seventh week after discharge, although the transfer of individual strains from patient to household contact was observed to occur, especially if the patient was a pharyngeal carrier. Presumably the addition to a household of a single person carrying a resistant strain of staphylococcus was not so great a hazard as the number of other contacts in the general population who were carrying organisms of similar resistance.

Since the number of antibiotic-resistant strains in a given segment of the population presumably increases with the number of individuals who have received antibiotic therapy, some means should be found to prevent the administration of antibiotics, without clear and sufficient indication, for a whole host of minor illnesses, diagnosed and undiagnosed. In addition, it would be profitable to explore technics of managing patients under treatment with antibiotics in order to prevent as much as possible the spread of resistant strains via hospital personnel to other patients.

SUMMARY

1. One hundred ninety-one cultures were taken from the noses and throats of 54 patients before and for eight to 21 weeks after discharge from a contagious disease hospital and 1,213 cultures from their 209 household contacts. Cultures were also taken from the hospital personnel at various times during the course of the study. The staphylococci present were studied with respect to their biological characteristics, their sensitivity to penicillin and aureomycin (and sometimes also to other antibiotics), and were typed by the bacteriophage method wherever possible.

2. Staphylococci were present in 74 per cent of the cultures taken from the patient at discharge from the hospital. This percentage decreased until after the fourth week it remained at approximately 36 per cent. Staphylococci were present in 33 per cent of the household contacts. This percentage did not vary significantly from week to week.

3. Among the staphylococci cultured, the percentages requiring for inhibition one or more units per ml. of penicillin were: 85 per cent in the case of hospital personnel, 88 per cent in the case of

patients at the time of discharge from the hospital, 36 per cent in the case of patients after the fourth week following discharge, and 30 per cent in the case of household contacts. The percentage of staphylococci requiring for inhibition 10 or more μg. per ml. of aureomycin were: 64 per cent in the case of hospital personnel, 78 per cent in the case of patients at the time of discharge from the hospital, 14 per cent in the case of patients seven weeks after discharge and later, and 7 per cent in the case of household contacts.

4. In seven of 54 families an individual strain was observed to have been transferred from the patient to a household contact, and in 10 families from a household contact to the patient. There was some indication that a strain was more likely to be transferred when it was carried in the throat than when it was carried in the nose.

5. It is postulated that antibiotic-resistant staphylococci may appear in the nose or throat of a person as a result of (a) treatment of that person with the antibiotic in question, (b) transfer of a resistant strain in the hospital, (c) transfer of a resistant strain in the community; and that all of these methods of spread of antibiotic-resistant staphylococci are important.

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REFERENCES

1. Beigelman, Paul M., and Rantz, Lowell A. The Clinical Importance of Coagulase-Positive, Penicillin-Resistant *Staphylococcus aureus*. *New England J. Med.* 242:353–358 (Mar. 9), 1950.
2. Elwood, J. Stanley. The Penicillin Sensitivity and Phage Types of Staphylococci Isolated From Hospital Patients. *J. Hyg.* 49:263–267 (Sept.), 1951.
3. Finland, Maxwell, Frank, Paul F., and Wilcox, Clare. *In vitro* Susceptibility of Pathogenic Staphylococci to Seven Antibiotics. *Am. J. Clin. Path.* 20:325–334 (Apr.), 1950.
4. Rountree, Phyllis M., Barbour, G. H., and Thompson, Edgar F. Incidence of Penicillin-Resistant and Streptomycin-Resistant Staphylococci in a Hospital. *Lancet* (Feb. 24), 1951.
5. Spink, Wesley W. Clinical and Biologic Significance of Penicillin-Resistant Staphylococci, Including Observations With Streptomycin, Aureomycin, Chloramphenicol, and Terramycin. *J. Lab. & Clin. Med.* 37:278–293 (Feb.), 1951.
6. Summers, G. A. C. Penicillin-Resistant Staphylococci. *Lancet* (Jan. 19), 1952.
7. Clarke, Suzanne K. R., Dalgleish, P. G., and Gillespie, W. A. Hospital Cross-Infections with Staphylococci Resistant to Several Antibiotics. *Lancet* (June 7), 1952.
8. Schneierson, S. S. Changes in Bacterial Sensitivity to Aureomycin and Chloramphenicol in the Course of the Past Three Years. *J. Lab. & Clin. Med.* 40: 48–57 (July), 1952.
9. Fisk, Alan. The Technique of the Coagulase Test for Staphylococci. *Brit. J. Exper. Path.* 21:311, 1940.
10. Barber, M., Hayhoe, F. G. J., and Whitehead, J. E. M. Penicillin-Resistant Staphylococcal Infection in a Maternity Hospital. *Lancet* 2:1120–1125 (Dec. 17), 1949.
11. Martin, T. D. M., and Whithead, J. E. M. Carriage of Penicillin-Resistant Staphylococcal Pyogenes in Healthy Adults. *Brit. M. J.* 1:173 (Jan. 29), 1949.
12. Rountree, P. M., and Thomson, E. F. Incidence of Penicillin-Resistant and Streptomycin-Resistant Staphylococci in a Hospital. *Lancet* 2:501–504 (Sept. 17), 1949.
13. Thompson, B. A., and Schwabacker, H. The Incidence of Penicillin-Resistant Staphylococci in a Semi-Closed Community. *J. Clin. Path.* 4:350–354 (Aug.), 1951.