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THE STAPHYLOCOCCUS: SEVEN DECADES OF RESEARCH (1885-1955)¹

BY C. E. DOLMAN

Abstract

The development of researches into *Staphylococcus pyogenes* is viewed in historical perspective at decade intervals over the period 1885-1955. Beginning when Lister's antiseptic spray ritual was about to be abandoned, the sequence of discoveries and attitudes is traced full cycle to the impending disenchantment with bacteriostatic agents. The early recognition of staphylococcal toxins was submerged by Metchnikoff's theories on phagocytosis, and Wright's on opsonins. The Bundaberg disaster drew attention again to the exotoxins; but almost simultaneously, Fleming's earlier work on the damaging effects of chemical antiseptics upon leucocytes culminated fortuitously in his discovery of penicillin. Before the antigenic properties of staphylococcus toxins could be exploited in a thorough clinical trial of toxoid and antitoxin, the sulphonamide and antibiotic era was upon us. Indiscriminate use of these agents inevitably provoked resistance to them by this versatile and ubiquitous pathogen, and led to the present mounting alarm at the intractability and prevalence of staphylococcal infections.

Among the more chastening chapters in the annals of microbiological research is the story of our apparently dismal failure to control the depredations of the staphylococcus. Repeatedly, fresh light has been shed upon the habits and habitats of these minute clustered spherules, and once-outmoded hypotheses about their metabolic mechanisms have been refurbished. Yet three-quarters of a century after Koch first noted their presence in pus, the staphylococci (like Francis Thompson's angels) "keep their ancient places", no less ubiquitous but still elusive, and (like Lucifer at least) shockingly endowed with apparently new, malign propensities.

The agents responsible for much more sinister threats to human health, e.g. smallpox, yellow fever, diphtheria, malaria, plague, typhus and typhoid fevers, and syphilis, have been largely brought under control and shorn of their former terrors, through such means as immunization of the prospective host, the destruction of vectors, the selective sterilization of transmitting media by chemical or physical means, and antibiotic therapy for already infected patients. But these measures, when variously applied to the control of staphylococcal infections, have been found wanting. Indeed, in many countries nowadays, hospitalization seems to entail a special risk of complications from such long-recognized conditions as puerperal mastitis, pemphigus neonatorum, and postoperative wound infections—according to the type of patient. Moreover, some hitherto unfamiliar clinical entities, such as staphylococcal pneumonia and enterocolitis, appear to be emerging, with derivations often as baffling as their outcome is devastating. A situation

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so challenging seems to invite a brief review of main landmarks in the panorama of staphylococcus researches. This will take the form of a brief conspectus at decade intervals over the last 70 years.

1885: Listerian Antisepsis

By 1885, Lister's prolonged researches into the causes and prevention of wound sepsis had won him the acclaim of Europe. Twenty years earlier, Semmelweis had died in a mental hospital, brokenhearted at the scorn heaped upon his doctrines about puerperal sepsis; and Lister, having been introduced to the work and writings of Pasteur, began to develop the theory that air-borne microbes, which the latter had shown were responsible for fermentation and decomposition of beer and wine, might also cause suppuration and putrefaction of wounds.

Lister's accomplishments stand out against a background of hopes first uplifted by the introduction of anaesthetics, then shattered by the ghastly mortality from sepsis in the lengthier and graver surgical undertakings which chloroform and ether made possible. Indeed, to quote Allbutt, "Suppuration, phagedaena, and septic poisonings of the system carried away even the most promising patients and followed even trifling operations. Often, too, these diseases rose to the height of epidemic pestilences, so that patients, however extreme their need, dreaded the name of hospital, and the most skilful surgeons distrusted their own craft. New hospitals or new wards were built, yet after a very short time the new became as pestiferous as the old; and even scrupulous care in ventilation and housemaids' cleanliness failed to prevent the devastation. Surgery had enlarged its freedom, but only to find the weight of its own responsibilities more than it could bear" (1). Or, as von Volkmann wrote, when a surgeon closed a wound, he was "like a husbandman, who having sown his field, waits with resignation for what the harvest may bring, and reaps it, fully conscious of his own impotence against the elemental powers, which may pour down on him rain, hurricane and hailstorm" (28).

Lister was always striving to improve his antiseptic and aseptic techniques, but would not abandon a device until convinced it should be supplanted. Then he was ready to admit his error. For example, at the time of the 1880 International Medical Congress, Lister's confidence was already waning in the dilute carbolic acid spray under which he and his disciples customarily operated; and his address to the gathering was mainly devoted to experimental observations on the healing of wounds, the antimicrobial properties of healthy animal tissues, and the protective role of blood clots peopled with migratory corpuscles. Yet in 1885 Lister was still using the spray, although its efficacy was widely challenged, and he had conceded that "the unconscious caretaker" might be wasted upon a relatively innocuous atmospheric flora. He finally gave up the spray in 1887, and told the 1890 International Medical Congress, "I feel ashamed that I should ever have recommended it . . ." (28).

Meanwhile, others had been investigating the sources of sepsis along different fronts. Ogston (46) had demonstrated in 1882 that "acute and

pyaemic abscesses always contain micrococci", consisting either of "chains interwoven with each other" or of groups "like the roe of a fish", and soon afterwards had named the latter *Staphylococcus*. In 1884, Rosenbach (48), isolated *Staphylococcus* in pure culture, and showed that it was commonly involved in wound suppuration, and was the causal agent of osteomyelitis. The year before, Metchnikoff had published his first report on phagocytosis (40). Thus, by 1885, the provokers and the functions of pus were under study, and the chief defenders of the animal body against an important invader had been revealed.

1895: Leucocytes and Leucocidin

In 1895, the civilized world mourned the death of Louis Pasteur, and his great eulogist, Sir Joseph Lister, became President of the Royal Society. By the shores of Southampton Water, Almroth Wright, Professor of Pathology at the Army Medical School, set about discovering a means of protecting the British Army from typhoid fever by immunization. His future disciple and successor, Alexander Fleming, then a lad of 14, left the seclusion of an Ayrshire village, and made his way to London. Meanwhile, Metchnikoff's researches on phagocytosis had evolved into a theory that inflammation was a biological defence mechanism (39). Any agent harmful to the polynuclear leucocytes would thus be inimical to the host. Van de Velde (52) had recently reported the presence of such an agent, which he termed *leucocidin*, in culture filtrates of *Staphylococcus pyogenes*, and in the exudate provoked in rabbits by intrapleural injection of live staphylococci. This substance caused marked degenerative changes in rabbit leucocytes *in vitro*, and when injected into rabbits, provoked the development of circulating antileucocidin (10).

1905: Antitoxin and Opsonin

By 1905, many of the toxic properties of staphylococcal filtrates had been explored, mostly in German laboratories. Von Lingelsheim (34) had reviewed the aetiology and therapy of staphylococcal infections, and reported the necrotizing and lethal effects of what he first called the *toxin* of staphylococci. Kraus (33) had observed the haemolytic action of certain staphylococcal cultures, and the varied susceptibilities thereto of different species of animal erythrocytes. Neisser (41) had noted the presence of antistaphylolysin in the blood of sick and healthy persons; while he and Wechsberg (42) had described the production of haemolysin and leucocidin, the assay of anti-haemolysin and antileucocidin in human or animal sera, and the pathological changes induced in the kidneys of experimental animals injected with staphylo toxin. The foundations of our present knowledge of staphylococcus toxins and antitoxins were in fact laid half a century ago.

The failure to apply such important findings was partly due to the powerful diversionary influence now emanating from Wright's laboratory at St. Mary's Hospital, London. Wright was so obsessed with "the bankruptcy of medicine" that in 1905 he appealed to the public in a newspaper article entitled "The

World's Greatest Problem", which stressed the need for more and better medical research (8). The pundits of Harley Street were particularly unenthusiastic about his culminating sentence: "That scientific knowledge which alone can avail in the conflict with disease is—practically all of it—still to seek". Nobody could deny that throughout the 40 working years left to him after penning these words, Wright sought manfully to make medicine solvent. In his view, the physician of the future would be an immunizator, aiming to call up the latent forces of the organism, especially through inoculations of heat-killed vaccines. With Douglas (57), he had revealed an important connection between humoral and cellular immunity mechanisms. The brilliant vigor of Wright's efforts to reinforce this link between his opsonins and Metchnikoff's phagocytes blinded him and many of his contemporaries to technical and dialectic fallacies. Yet one of his last papers contained a remarkable recantation of some of the presuppositions on which the rationale of opsonic index determinations was based (55).

Certain strains of *Staphylococcus* proved, perhaps unfortunately, very suitable for these opsonic experiments. Their phagocytosis was so undeniably evident *in vitro* that any observer could be led to dismiss as irrelevant such toxic metabolites as e.g. the leucocidin, whose deleterious effects upon phagocytosis in staphylococcal infections might far outweigh any opsonic benefits accruing from vaccine therapy.

1915: War Wound Sepsis

In the foreground now is the carnage of World War I. By 1915, Wright and a team of devoted associates from the Inoculation Department at St. Mary's, including Fleming, Leonard Colebrook, and John Freeman, were already immured in problems of wound sepsis. Gas gangrene and tetanus took a fearful toll, and all varieties of pyogenic microbes wrought havoc, so that the Surgeon General was moved to declare, "We have, in this war, gone straight back to all the septic infections of the Middle Ages". But on the whole, staphylococci were found too much everywhere to be reckoned a major menace. Wright launched a campaign to deter surgeons from stuffing wounds with chemicals, which not only destroyed leucocytes, but hindered their access to the microbes. "Leucocytes are the best antiseptic" was his dictum, and wound treatment must provide optimal conditions for their functioning (8). Wright's wartime experiences only confirmed his views on the paramount importance of the healthy leucocyte in the bodily defence against infection, whether by Welch's bacillus or by staphylococci. He never altered this belief.

In 1914, little noticed and long overlooked, two papers had appeared, which illustrated the versatility of *Staphylococcus*. Nicolle and Césari (43), reported from the Pasteur Institute that staphylococcal strains isolated from infected farm animals closely resembled cultures from human lesions, even in respect of the necrotizing and lethal properties for rabbits and guinea pigs of their

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filtrates. On the other side of the world, Barber (3) attributed sporadic attacks of gastroenteritis affecting visitors to a farm in the Philippines to the presence of staphylococci in the milk of one particular cow.

1925: Denunciation of Intravenous Antiseptics

During the war and postwar years, the disappointing failure of old and new antiseptics to cleanse deep wounds, and the contrastingly "laudable" properties of fresh pus, were analyzed and accounted for in many ingenious ways, by Wright and Fleming. The latter adapted Wright's slide cell device (56) to the testing of chemical antiseptics in the presence of infected blood, and showed that all such agents then available destroyed the phagocytic power of the leucocytes more readily than they killed the microbes present in the mixture (25). In these slide cell experiments, Fleming customarily used a strain of *Staphylococcus* as test organism. The principles thus demonstrated helped to discountenance the prevailing tendency to administer antiseptics intravenously in desperate cases of staphylococcaemia. But, on the whole, progress seems to have been halting or marking time during this period. The march of events in the following decade more than made up for this.

1935: Bundaberg and Penicillin

The death knell of antiseptic therapy appeared to be tolling in 1925; but soon, trumpets were sounding from several directions. By an irony of circumstance, Fleming's tentative clarion call in 1929 was to carry the farthest and echo most. Persons fortunate enough to have been working with Fleming at the time of penicillin's discovery, or shortly after, will recollect the almost childlike eagerness with which he displayed the famous mold-contaminated plate to "The Old Man" (Sir Almroth Wright), to colleagues, and to students. He hoped for great things of this inhibitory factor, particularly in the treatment of boils and carbuncles—for was it not a *Staphylococcus* culture that showed lysis near the fungal growth?—and filtrates were applied topically in a few cases. Despite ribald and derisive comments from The Old Man and others, administration by mouth was also considered. One recalls, for example, helping to make a batch of "mould juice" (as it was irreverently termed in Fleming's laboratory 25 years ago) for administration to an elderly arthritic, whose affliction was held due to enterococci. The patient's bravery in swallowing three pints of the beverage was not rewarded by beneficial results. The erratic potencies and lability of these early crude preparations led to the setting aside of penicillin as a therapeutic agent. Besides, alternative possibilities for dealing with staphylococcal infections were discernible on the horizon.

In 1928, at Bundaberg, Queensland, 12 children had died within 15 to 34 hours of receiving an injection of diphtheria toxin-antitoxin mixture to which no preservative had been added. Among those appointed to investigate the disaster was Burnet, a young bacteriologist from Melbourne, who concluded

that the mixture had become contaminated with a toxin-producing *Staphylococcus* (31). In 1930, soon after the appearance of the first of several papers by Burnet on the production and properties of this formidable exotoxin (4), Professor Fleming suggested to the present writer that this agent, properly detoxified, "might be useful in the boil clinic" at St. Mary's Hospital. In 1931, emigration to Canada interrupted the enquiry thus instigated; but enough had been done to justify continuing *Staphylococcus* researches in the Connaught Laboratories at Toronto.

By 1935, many reports on staphylococcus toxin, toxoid, and antitoxin had issued from laboratories in Australia, Canada, and England. These established the conditions for *in vitro* production of highly potent toxin (5, 12); for the formol detoxification of the product (6, 19); for titrating the combining power of the toxoid (19); and for assaying the antitoxin in terms of an International Standard Unit (29). Arrhenius' comment of many years before, that "staphylolysin behaves in a very peculiar manner", was soon amply confirmed; and the haemolytic effects produced by staphylococcal cultures on blood agar plates, or by their filtrates on erythrocyte suspensions, were recognized as due to multiple factors, even yet not all elucidated (13). In particular, the so-called β -toxin was differentiated from the necrotizing and acutely lethal α -toxin (27). In yet another direction, Jordan, Dack, and others at Chicago confirmed and extended Barber's observations of nearly 20 years before by showing that filtrates from appropriate strains of *Staphylococcus* could provoke symptoms of acute gastroenteritis within a few hours of their ingestion by human volunteers (9, 30). In Toronto, this food poisoning factor, or enterotoxin, was shown to be distinct from the α -toxin (16).

Clinicians were not kept waiting for all the unfolding laboratory complexities to be resolved before having opportunities to try out the toxoid and antitoxin in their patients. By 1935, toxoid had given encouraging results in localized staphylococcal infections (14, 17); while antitoxin had apparently aided recovery in severe and even desperate cases of acute and generalized infection, treated in Toronto and Montreal—the latter group under the supervision of Professor E. G. D. Murray (15).

Numerous difficulties were encountered in the manufacture and administration of these products; in the unravelling of the immunological principles involved; and in the selection of patients, the provision of controls, and the assessment of results. Some physicians could not understand how patients suffering from intractable furunculosis often displayed little or no increase in circulating staphylococcus antitoxin, whereas a few small subcutaneous injections of toxoid usually raised the antitoxin titer and brought an end to the boils. Many surgeons expected small dosages of antitoxic serum to be effective in patients riddled with abscesses, in sites perhaps as inaccessible to the circulating antitoxin as to their pus-letting scalpel; or hoped that large amounts of antitoxin might still avail in patients whose vital centers and viscera were irreparably damaged already by toxins. But in the midst of efforts to clarify the resulting confusion, suddenly there

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seemed no purpose in trying. For Dogmak's discovery of the chemotherapeutic properties of the dye Prontosil in 1935, and the quick identification of the active portion of its molecule, ushered in the sulphonamide era.

1945: Apotheosis of Bacteriostatic Agents

Admittedly, the bacteriostatic agents have proved in many respects a great boon to medicine; but when used irresponsibly or unscientifically—on the principle that pills are much easier to take and administer than antigens and antitoxins—they may do more harm than the intravenous germicides of earlier decades. Excessive amounts can be as toxic for leucocytes, kidney, and liver as any of the older antiseptics; while in smaller, sustained dosages, they may interfere with the host's immunity mechanisms, and induce heritable drug resistance in the invading microbes. Nor can these drugs affect toxin already produced, or still to be produced, by microorganisms surviving in the tissues. Although these handicaps of the new chemotherapy were predictable or soon observable, they are not easily remediable. Just as the time seemed ripe for thoroughly testing the theoretical advantages of combining bacteriostasis and antitoxic immunity, World War II broke out.

This time, the desperate cry for a remedy for the wound infection problems of earlier wars brought forth a wonderful response. Soon after Florey and Chain had shown at Oxford in 1940 how penicillin could be concentrated, the manufacture of this antibiotic had top priorities; and by 1945, the golden droplets of "mould juice" gleaned so uncertainly from the gray-green fungus in small flasks at Paddington 15 years before were being harvested from giant vats in North America at the rate of thousands of gallons weekly. The activity of the product was still assayed against a susceptible strain of *Staphylococcus*.

Waksman's discovery of streptomycin in 1943 began to raise expectations in some quarters that if enough trained technicians diligently searched the soil, other antibiotics might soon emerge to master all bacterial pathogens insusceptible to penicillin and streptomycin. There were many who even contended that bacteriology had seen its heyday, and that enterprising microbiologists should turn to the viruses. In such a climate one could still prophesy; but to stress the role of toxins in staphylococcal infections was like crying in the wilderness.

On the other hand, staphylococcus food poisoning was obviously not amenable to antibiotics, and by now had become recognized in North America and (more tardily) in Great Britain as a very common entity. The wartime prevalence of food-borne outbreaks of acute gastroenteritis afforded an incentive for further exploration of this problem. From the outset, a major difficulty in working with staphylococcal toxins has been to sort out the respective properties of the various haemolysins, and especially to differentiate between their effects and those of the enterotoxin on experimental animals. Now, about 10 years after the enterotoxin had been distinguished from the α -toxin by ingestion experiments on human volunteers, its separate identity

from the β -toxin was likewise demonstrated (18). As this method of testing is too inconvenient and hazardous to be warranted except to settle crucial questions, the kitten test for enterotoxin (21) was also re-examined. The need to avoid false positive reactions due to β -toxin was stressed, and minor modifications in the test were suggested. In the nearly 20 years since the feline reaction was first described, various alternatives have been proposed—involving monkeys, piglets, chicks, baby mice, decapitated frogs, and isolated portions of rabbit intestine—but all proved disappointing. Some imperfections of specificity and sensitivity probably remain inherent in the kitten or cat test for enterotoxin; but recently it has been favorably reappraised by Matheson and Thatcher (38).

The complexity of *Staphylococcus* was again exemplified in 1938 by the identification of a distinct γ -haemolysin in filtrates of certain strains (51). In the next decade, this analysis was to be carried further, and the existence of δ and ϵ -lysins postulated (53, 36, 23). The apparent nephrotoxic properties of the β -toxin (20), the dermonecrotic action of the δ -toxin (36), and the antigenicity of the specific coagulase (47), were to re-emphasize to manufacturers of staphylococcal antigens the importance of selecting polyvalent strains.

Finally, at the close of the decade, Wilson and Atkinson (54) developed a method of typing staphylococci by means of bacteriophage, first described in 1942 by Fisk (24), which was soon to prove most useful epidemiologically.

1955: Disenchantment and Dismay

This last decade began full of confidence that *Staphylococcus* as a menace to man would soon be laid low. The delusion has been rudely dispelled. Today, staphylococcal infections appear more prevalent, more virulent, and more unavoidable, than they were a quarter-century ago, in the prepenicillin area. Moreover, these infections seem to have assumed the status of an occupational or environmental disease in places where one might least expect to find them, namely hospitals. The final touch of tragic irony in the dénouement is that whereas penicillin-resistant strains of *Staphylococcus* were seldom encountered when supplies of this antibiotic first became unrestricted soon after the war, the majority of hospital strains are now resistant to it.

The current incidence and types of staphylococcal infections inside and outside hospitals are difficult to assess, if only because hospital administrators, and the medical and surgical staffs, display attitudes ranging from that of the alarmist who regards a minute pustule on a baby's bottom as significant, to that of the escapist who avoids admitting the existence of any situation serious enough to involve his institution in possible discredit or a damage suit. To attempt statistically valid comparisons between the situation now and that prevailing a generation or even a decade ago would be manifestly futile. The incidence of staphylococcal infection, calculated as a percentage of total admissions to hospital, or of total surgical operations, may have increased only in relation to all other types of infection. Nevertheless, we must acknowledge the widespread impression of a recent change for the worse

in hospital experience with staphylococcal infections, which is only partly reflected in the medical literature. Troublesome though seldom fatal outbreaks among infants and nursing mothers have brought closure of maternity wards; while anyone professionally connected with a large hospital can recount tragic instances of fulminating infection. For example, a patient hospitalized for pneumococcal pneumonia, and recovering therefrom, died a few days later of staphylococcal pneumonia. A simple appendectomy in a healthy young man (a physician) resulted in septic thrombosis, osteomyelitis of vertebrae, extradural abscess, and paraplegia; while paronychia in a healthy young woman (also a physician) ended within a week in fatal staphylococcal meningitis. These things should not be; yet such examples, culled from local sources, could be matched and multiplied elsewhere in North America, and in the British Isles, Scandinavia, or Australasia. The situation is superficially reminiscent of that prevailing almost a century ago, when Florence Nightingale commented: "It may seem a strange principle to enunciate as the very first requirement in a Hospital that it should do the sick no harm" (44).

These final paragraphs may fittingly consider how it has come about that the latest decade of *Staphylococcus* researches, which dawned so promisingly, should be ending in an atmosphere of somber bafflement. The problem basically involves host-parasite relationships, and can therefore be dealt with from the standpoints of the parasite, of the host, and of the modes of transmission. Considering first the parasite, few would dispute that the indiscriminate use of penicillin during the first years after it became generally available was largely responsible for the growing preponderance of resistant strains. Exposure of so ubiquitous and versatile a parasite to such an inhibitory agent—by every route from inunction, irrigation, and inhalation to injection and ingestion—inevitably resulted in a process of natural selection favoring strains which can produce penicillinase. Alternatively or additionally, exposure of staphylococci to penicillin (or other antibiotics) may induce new, resistant mutants to develop. These processes presumably account for the penicillin-resistant staphylococcal flora developing in war wounds after prolonged penicillin treatment, noted already in 1946 by North, Christie, and Rank (45); and for the observations of Rountree and Thomson only three years later (49), that the nasal carrier rate of penicillin-resistant strains of *Staphylococcus* among 200 hospital staff members was 32%, in contrast to 4% in a similar group of blood donors.

Although there is no laboratory evidence that antibiotic-resistance in staphylococci is yet associated with new or exalted toxigenic capacities, this may be due merely to the inadequacy of present methods for detecting all the complex properties involved. Another worrisome possibility is that mutant strains could develop which flourish only in the presence of low concentrations of certain antibiotics.

Closely connected with these contingencies are the alterations in the potential host resulting from use and abuse of antibiotics. The effects of

administering an antibiotic by mouth are by no means confined to inhibition of a susceptible pathogen. Other changes may be provoked in the intestinal flora, so that potential pathogens, normally held in check, can flourish and cause disorder. What holds true for *Candida albicans*, for example, could equally apply to *Staphylococcus*, which is now known (through development of special media) to inhabit some intestines in significant numbers. Such organisms, multiplying unimpeded by antibiotics or by bacterial competitors, might soon elaborate dangerous amounts of the α -, β -, or enterotoxin. Though α - and β -toxins are apparently not absorbed from the normal intestinal tract, they might occasionally traverse an intestinal mucosa denuded of its customary flora. Similar mechanisms could conceivably operate in the upper respiratory tract. The bacteriologist and clinician together should be able to settle eventually whether the acute toxæmias of staphylococcal enterocolitis or bronchopneumonia may thus be explicable. Meanwhile, there is a sound middle course between that of the optimist who believes that every strain of *Staphylococcus* has its Achilles' heel, and must therefore be challenged in succession with every antibiotic weapon available, and that of the fatalist who believes, so to speak, that a patient's number is up if the strain attacking him has his number on it. This course surely includes the intelligent application, with proper laboratory controls, of the principles of both bacteriostasis and antitoxic immunity.

The problems of transmission, i.e. the epidemiology of staphylococcal infections, can only have brief consideration here. The human nose is now accepted as an important reservoir for *Staphylococcus pyogenes*. Attention was first drawn to this point 20 years ago (17), and there are now numerous reports on its significance (35, 26, 11, 50). Again, new light has been thrown on the transfer of staphylococci between the milk of nursing mothers and the alimentary canal of their infants (22); on the rapidity with which the nasopharynx and faeces of infants harbor staphylococci derived from their environment (37); and on the ready conveyance of mastitis to mothers by infants with air-borne staphylococcal infections of the nose and throat (7).

Efforts to cope with the intransigence and resourcefulness of *Staphylococcus* entail extremely close analyses of hygienic practices in hospitals. The miscellaneous potential sources of infection, e.g. air and dust, bedding and mattresses, baths and laundry baskets, surgeons' gowns and anaesthetic apparatus, must be not only scrutinized bacteriologically, but dealt with appropriately (32, 2). Unfortunately, control problems are much aggravated by the rapid circulation of employees, whose proliferation as a result of shortened working hours and of more specialized medical and nursing care, multiply the chances of contacts between patients and unskilled, partly trained, or careless persons. The situation will eventually yield to a better understanding and a more enlightened imagination on the part of all, including the highest ranks of clinicians, especially when the notion of sheltering under the antibiotic "umbrella" has been discarded as finally as the ritual of Lister's spray.

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In the acquisition and dissemination of relevant data, the bacteriologist will doubtless play as full a part in future *Staphylococcus* researches as he has done over the past 70 years. The adversary is formidable, but there is no need for dismay. This review was not intended to point a clear path straight through the woods, but was undertaken in the belief that backward-glancing often clears the eye, adjusts the perspective, and brings encouragement. We have come a long way in what is, after all, only the lifetime of an average man.

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