Chapter 1

Antibiotic Policies—A Historical Perspective

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1. ORIGINS OF ANTIBIOTIC POLICIES

1.1. The pioneers

In 1945, at the end of World War II, Professor Sir Alexander Fleming (as he had then become) was asked by Butterworth, the medical publishers, to write a book on penicillin. He refused, on the grounds that he was too busy and that as a laboratory worker, he would have been unable to place penicillin therapy in a proper perspective in relation to other forms of medical and surgical treatment. However, he did agree to edit a book—and produced a volume (Fleming, 1946a) which is now something of a rarity—bringing together contributions from many of those who had gained experience of the compound during its early years of scarcity. Furthermore, he wrote an introductory chapter in which he overcame his modesty and set out some general rules for penicillin treatment (Fleming, 1946b). First, he wrote, it should be used only for the treatment of those infections caused by penicillin-sensitive microbes. His list of these runs: staphylococci, *Streptococcus pyogenes, Streptococcus viridans*, some anaerobic streptococci, pneumococcus, gonococcus, meningococcus, and so on. He also points out the importance of acquired resistance even though there was little of it at the time. However, despite the many casualties on this list, the principle remains sound. Second, the antibiotic must be given by an appropriate route, in adequate dosage, for an appropriate period of time—and despite uncertainties, the principles again remain true. *En passant*,

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he made a plea that doctors should resist patients' and press demands for penicillin to be used for a variety of inappropriate purposes, and listed cancer, tuberculosis, rheumatoid arthritis, psoriasis, and almost all the virus diseases among the many conditions that he had personally been asked to treat. Patients and the media may now be better informed, but irrational demands continue. He also mentions the problem of toxicity, dismissing it promptly in the context of penicillin, although L. P. Garrod gives a more balanced account in an other chapter (Garrod, 1946). Finally, Fleming discusses the assay of penicillin in blood, cerebrospinal fluid, urine, pus, and sputum and so can even be considered to have indicated the importance of pharmacokinetics (Fleming, 1946c). It seems to me that in his book, albeit in the somewhat discursive manner characteristic of the times, Fleming had defined rational therapy in terms of the infection to be treated, the causative organism and its *in vitro* antibiotic susceptibility and the importance of pharmacology including toxicity.

One more aspect of Fleming's book deserves attention in the context of the development of the concepts of antibiotic policies. In a chapter on the prophylactic use of penicillin, Porritt and Mitchell (1946) discuss the comparative merits of sulfonamides and penicillin for the prevention of infection in war wounds. The clinical trial conducted to clarify the issue would not nowadays commend itself to those who regulate most of the day-to-day relevance out of such things, but it did lead to the abandonment of sulfonamides and their replacement by penicillin, a policy that I found still in operation 40 years later! Was this indeed the first antibiotic policy?

1.2. Early developments

In a chapter that I wrote in 1979 (Phillips, 1979), I argued that an antibiotic policy assumes that antimicrobial therapy will be rational for the individual patient—"that the antibiotic chosen is likely to cure or prevent infection; that the pathogen is sensitive to it in vitro; that the risk of side effects is minimised; and that pharmacological and pharmaceutical properties are appropriate." Many guides based on these considerations were produced in the 1970s (Bint and Reeves, 1978; Geddes, 1977; Wise, 1977). A policy is something superimposed on such rational use, taking into account the risk of development of resistance, cost, simplicity, and the personal preferences of the prescribing clinician (Figure 1). It depends on pragmatic consensus, but even that should not prevent a clinician ignoring it in what he believes to be the best interest of an individual patient.

This point of view represents the teaching of Fleming and the early pioneers as digested and passed on by my own teachers at St Thomas' Hospital, notably Professor Ronald Hare (who wrote his own version of the discovery of penicillin, based on a ring-side seat at St Mary's Hospital in the 1920s) and

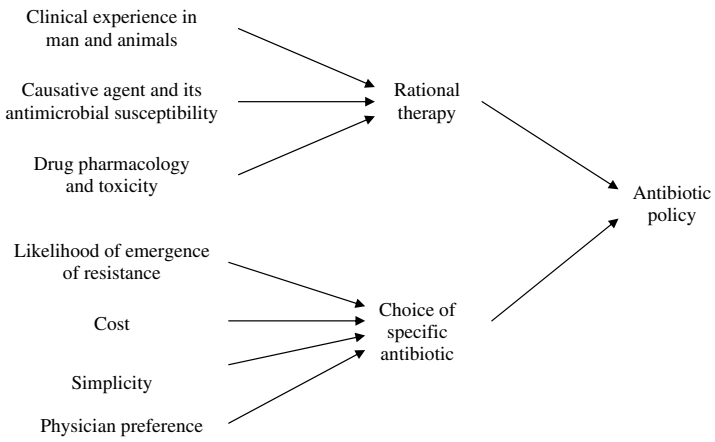

Figure 1. Components of an antibiotic policy (based on Phillips, 1979).

Dr Mark Ridley (who sadly died at a young age). Their views were in turn much influenced by the work of Dr Mary Barber, initially in Hare's department at St Thomas' and later at The Hammersmith Hospital, and co-author with L. P. Garrod of an influential textbook "*Antibiotic and Chemotherapy*," first published in 1963 (Barber and Garrod, 1963).

There seems little doubt that the first civilian antibiotic policies came into being with the emergence of the "Hospital Staphylococcus" in the late 1950s (Garrod and O'Grady, 1971; Phillips, 1979). At St Thomas' Hospital a Sepsis Committee was set up in 1959 "to review hospital infection and to suggest methods for its prevention" (Phillips, 1979). One of the major approaches to control, related to the use of antibiotics and the recommendations were based to a large degree on the specific experience of Mary Barber and her colleagues (Barber and Burston, 1955; Barber and Dutton, 1958; Barber and Garrod, 1963; Barber and Rozwadowska-Dowzenko, 1948; Barber *et al*., 1958). For example, she recommended the use of erythromycin only in combination, as did Lowbury (Lowbury, 1957), and for a number of years our clinicians prescribed it only with a full dose of novobiocin. It is of interest that none of these clinicians complained about the toxicity of novobiocin and whether their patients did must be a matter of conjecture! The policy for the treatment of *Staphylococcus aureus* infection in operation from 1960 until 1967 (Phillips and Cooke, 1982) involved the use of penicillin for the 30–35% of hospital-isolates still susceptible to penicillin, and erythromycin plus novobiocin for the remainder unless there was resistance to either of them, in which case methicillin or later cloxacillin was to be used. Thus in the years 1959–60 we moved from a policy of free use of any antistaphylococcal agent, to restriction (of erythromycin and then methicillin/cloxacillin)

to use of combinations (erythromycin plus novobiocin). Prof. (later Sir) Robert Williams and his colleagues, in their influential book "*Hospital Infection, Causes and Prevention*" (Williams *et al*., 1960) listed restriction, diversification, rotation, and combination as the measures available to those who devise antibiotic policies, and we had in some measure used all four. By 1967, it had become clear that, after its first appearance in the early 1960s, methicillin resistance, despite its early recognition, had not become a problem (Cookson and Phillips, 1988; Jepsen, 1986), and so erythromycin and novobiocin, and, for good measure, fusidic acid were restricted and methicillin, cloxacillin or, later, flucloxacillin were made freely available.

Did policies of the kind introduced in my own hospital overcome the problem of staphylococcal resistance? We and others, in many parts of the world, thought so (Barber *et al*., 1958, 1960; Goodier and Parry, 1959; Hinton and Orr, 1957; Kirby and Ahern, 1953; Lepper *et al*., 1954; Lowbury, 1955; Phillips, 1979; Phillips and Cooke, 1982; Ridley *et al*., 1970; Shooter, 1957, 1981; Wallmark and Finland, 1961)! Rosendal and her colleagues in Denmark, attributed the changes to a diminished use of streptomycin and tetracycline for the treatment of staphylococcal infection (Rosendal *et al*., 1977). At its worst, the "Hospital Staphylococcus" was resistant to penicillin, streptomycin, tetracycline, chloramphenicol, erythromycin, novobiocin, and neomycin, and if fusidic acid was used, it often became resistant to that too. It was never resistant to methicillin, although other less common and less multiresistant strains were (Figure 2).

The early restriction of erythromycin was accompanied by a fall in resistance rates from 18% to 4%, returning to 20–25% only after 3-years use of erythromycin and novobiocin, an example, we thought, of the delaying effect on the emergence of resistance due to antibiotic combination. Restriction of methicillin/cloxacillin had, again we believed, resulted in our having less than 2% (and usually much less) of isolates resistant to these drugs. However, it was then made clear to me by the Director of the National Staphylococcal Reference Laboratory, Dr M. T. Parker, that similar events had been occurring nationally even in hospitals that had no antibiotic policies (Parker, 1971). The subsequent demise of the "Hospital Staphylococcus" from the mid-1960s onwards (Ayliffe *et al*., 1979; Bulger and Sherris, 1968; Gransden *et al*., 1982; Shooter, 1981), in the context of a relaxation of our policies reinforced the conclusion that much of what we observed had more to do with the natural waning of an epidemic than to our infection control and antibiotic policy interventions. Prof. Mouton and his colleagues were not alone in drawing attention to paradoxes (Mouton *et al*., 1976). The unwisdom of attributing past events to uncontrolled and assumed causes was an early lesson which continues to be ignored (Phillips, 1998a, b)! This is not to say that some resistance was not driven by antibiotic use. Another personal experience relates to chloramphenicol-resistant staphylococci which

	Year																			
	1958	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77
P	80	62	75	63	72	63	72	75	62	73	75	72	78	74	79	82	81	79	85	83
PST	20	32	35	25	31	32	18	24	14	9	5	7	7	8	5	4	3	0.4		
M								0.1	0.2	0.5	1	2	1	1	1	2	1	0.4	0.4	0.05
E	18	4	4	2	20	24	15	17	4	3	4	9	3	3	2.5	5	4.5	5	6	7
L														0	0.3	0.3	1	0.5	0.4	0.5
F													0	2	2.5	2	2	2.6	3.4	4
Policy	1	2	3							4				5				6		
	Year																			
	1978	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97
P	85	85	84	86	76	63	92	84	88	81	50		83	92	90	89	93	95	84	87
M	0	1.2	0.9	0.9	3	0	21	8	3	0	0		0	6	3	2	10	39	49	42
E	4	6	7	6.4	8	5	25	16	6	3	5		10	10	15	7	13	45	46	47
G	2	1.8	1	2	8	0	17	4	6	3	0		4	4	5	4	20	26	13	10
C			0	0	3	0	0	0	0	0	0		6	6	10	2	5	44	43	44
Policy							7							8						

Figure 2. Trends in antibiotic resistance of *Staphylococcus aureus* isolated from inpatients in St Thomas' Hospital 1958–97 and antibiotic policy changes.

Notes: Policy: (1) free use; (2) erythromycin restricted; (3) penicillin, erythromycin plus novobiocin, and methicillin/cloxacillin; (4) penicillin and methicillin/cloxacillin, erythromycin, novobiocin, and fusidic acid restricted; (5) relaxation with increasing use of clindamycin and fusidic acid; (6) decreasing use of clindamycin because of pseudomembranous colitis; (7) increased use of vancomycin because of MRSA; and (8) further increased use of vancomycin due to successive epidemics of MRSA.

Antibiotic resistance (each figure represents the % resistant during the year): P, penicillin; PST, penicillin, streptomycin, and tetracycline combined (The Hospital Staphyloccus); M, methicillin (MRSA methicillin/multiply-resistant *S. aureus*); E, erythromycin; L, lincomycin; F, fusidic acid; G, gentamicin; C, ciprofloxacin.

Sources: Based on Phillips, 1980 (1958–77), Gransden *et al*., 1982 (1978–81), Phillips and King, 1979 hospital bacteraemia isolates only, unpublished (1982–1997).

were isolated only in the wards of a particular surgeon who regularly used the drug (with no untoward effects on his patients) and which disappeared immediately upon the surgeon's retirement.

1.3. Extension of policies

The work of Dr Maxwell Finland and his colleagues in Boston (Finland, 1970; Finland and Jones, 1956; Finland *et al*., 1959) and work in specialised units such as the Birmingham Accident Hospital (Lowbury, 1955) extended interest to the development of resistance among Gram-negative organisms. One of the best known examples of control of resistant organisms by total antibiotic restriction—klebsiella infection in a neurosurgical unit—was reported by Price and Sleigh (1970). This expansion of interest in organisms other than *S. aureus*, together with the introduction of new classes of antibiotics, at ever increasing

costs, in the 1950s and 1960s, led to a further justification for the introduction of antibiotic policies based on the understandable confusion of clinicians in the face of so many similar or to them apparently identical drugs. As early as 1955, Prof. L. P. Garrod concluded that "the choice is now so wide, and the indications are so complex, that few clinicians can keep fully abreast of knowledge about them" (Garrod, 1955).

These developments had already led to the creation of yet another type of committee, often called the Antibiotics Committee, which, at St Thomas', was set up in 1960 to "consider, continually review, recommend and give information on antibiotic policy in the hospital" (Phillips and Cooke, 1982). It continued to do this for 30 years, taking all of the considerations so far mentioned into account, including costs, until its work was taken over by a more general Use of Drugs committee, an example of a general Formulary Committee. I believe that it is fair to say that antibiotics were not high on the agenda of such committees since the amount expended on them was relatively little in comparison with drugs used to control chronic ill health, both physical and mental: in 1980, antibiotics accounted for only 13.4% of hospital drug costs (Cooke *et al*., 1983). Whether for that or other reasons, the amount of effort given to controlling antibiotic use declined, and there was a hiatus before the renewed efforts described elsewhere in this volume, largely related to the increasing prevalence of resistance and an increased perception that it was a problem.

There were sceptics in relation to the ethics of antibiotic policies throughout. Selkon (1980) agreed with many that general policies involving restriction were an intolerable affront to clinical freedom, led to suboptimal treatment for individual patients, and had "rapidly lost credibility." He further argued that they complicated antimicrobial chemotherapy. Finally he described the policy in Newcastle where clinicians reserved the right to prescribe whatever antibiotics they thought appropriate, with the pharmacist informing the microbiologists of potentially harmful prescribing, and the microbiologists intervening on an individual basis. Perhaps the more *laissez faire* attitude that we developed in the 1970s (Figure 2) when there were few problems, was not very different from this.

1.4. Policies for all

The original antibiotic policies, arising as they did from problems of control of infection with resistant bacteria in hospitals, were strictly for application within the individual hospitals that produced them. They were often amplified by policies specific to units within hospitals. The Burns unit in the Birmingham Accident Hospital was one of the pioneers (Lowbury, 1955; Lowbury *et al*., 1957). One of our first restricted policies was developed for use within our Renal Unit: a specific example from that policy was the use of

vancomycin administered in weekly dosage to anephric patients with staphylococcal infections around indwelling shunts for renal dialysis (Eykyn *et al*., 1970), together with minimal use of the first-generation cephalosporin, cephaloridine, and of gentamicin for other severe infections (Phillips,1981). Interestingly, we had no vancomycin-resistant enterococcal infections at the time of their first description in a neighbouring teaching hospital and for many years thereafter. Later we produced a policy for our Urology Unit (Casewell *et al*., 1981).

A final addition to our Antibiotic Committee was a general practitioner, when it became clear that resistance was becoming a problem in the community—for example, that *Escherichia coli* was becoming resistant at a rate of 1% per annum, to what had been considered first line agents for urinary tract infection (Phillips *et al*., 1990). It also had become generally recognised that most antibiotics were used in the community, and, furthermore, were not particularly rationally used (Cooke *et al*., 1985).

The apparent success of particular policies led to demands for their dissemination to other hospitals and even to NHS Regions. Ridley produced his "*Pocket Guide to Antimicrobial Chemotherapy*" based on the St Thomas' guide and policy in 1971 (Ridley, 1971), and the microbiologists of the South East Thames Regional Health Authority produced their "Guide to the use of antimicrobial drugs" in 1977 (SETRHA, 1997). However, many felt that a lack of local ownership of such guides, and the need to compromise, made them little more than the guides they purported to be and not true policies. Lowbury summed up the problem when he pointed out in 1975, that "in Dudley Road Hospital (Birmingham) a severe wound infection could be treated with kanamycin (whereas) in the Burns Unit of Birmingham Accident Hospital, kanamycin would be an incorrect choice," arguing for purely local policies (Lowbury, 1957). Nevertheless, at the other extreme, some countries, such as Czechoslovakia (Modr, 1978), developed and applied national policies.

1.5. A fundamental approach

In the 1960s, there was some discussion of the possibilities for alternative approaches to the control of resistance. Pollock (1960) suggested that as well as reducing selection pressures, we might try to prevent mutation and recombination. There have been other calls for reversal of resistance by genetic means, although I have expressed reservations in relation to potential methods involving genetic engineering (Phillips, 1998a, b). I hope that I shall be proved wrong!

I have also called for fundamental rethinking about the possibility of controlled trials of antibiotic policies. Too often are we satisfied by our attributions of epidemiological trends in resistance to arbitrarily chosen—even if

apparently logical—trends in antibiotic usage (Phillips, 1998a). Perhaps a few more charts relating increases in antibiotic resistance to sales of bananas and the like, might be helpful.

2. PRACTICAL APPLICATION OF POLICIES

2.1. Surveillance of antibiotic usage and resistance

Surveillance of resistance grew out of such studies as those carried out by Finland and his colleagues at the Boston City Hospital (Kislak *et al*., 1964; McGowan and Finland, 1974a; Wallmark and Finland, 1961), followed up by specific surveys of antibiotic usage and resistance in many parts of the world (Kayser, 1978; Lawson and MacDonald, 1977; Moss *et al*., 1981; Mouton *et al*., 1976; Sheckler and Bennett, 1970; Swindell *et al*., 1983). O'Brien and his colleagues reported specifically international comparisons (O'Brien *et al*., 1978).

Having been appointed Infection Control Officer at St Thomas' Hospital in 1963, I was responsible for the collection of statistics on wound infection, visiting all of the hospital wards weekly as well as carrying out myself the phage typing of all hospital *S. aureus* isolates. My main finding was that although the prevalence of hospital staphylococcal infection did not decline, the prevalence of multiply resistant *S. aureus* certainly did! Whether this "result" fulfilled the expectations of the Sepsis Committee must be doubtful. However, another of the essential features of a policy had been put in place—the collection of statistics on the prevalence of resistance (Figure 2), continued from 1958 until my retirement in 1996 (Gransden *et al*., 1982; Phillips, 1980; Phillips and King, unpublished; Ridley *et al*., 1970). Something else was learned from this exercise, that the collection of statistics has absolutely no effect to the good on the prevalence of resistance, and this probably led to the addition of an Infection Control Nurse to a nascent Infection Control Team, as part of a national development.

For a time during the 1970s we too collected statistics on antibiotic usage and attempted to relate them to the prevalence of resistance (Gransden *et al*., 1982). This turned out to be a period of respite when epidemigenic strains of *S. aureus* virtually disappeared from our wards (Gransden *et al*., 1982) and there appeared to be little correlation between usage and resistance, and so we abandoned the collection—just before epidemic methicillin-resistant strains returned, apparently to stay (Figure 2).

2.2. Ensuring compliance

The Antibiotics Committee learned a great deal about the development and application of antibiotic policies and their audit (Phillips and Cooke, 1982).

Mary Barber, a formidable lady, showed us the importance of authority and leadership! We further recognised the importance of the inclusion on the committee of influential physicians and surgeons on the staff of the hospital. They were very important in ensuring support from the staff in general, who were always consulted formally in full committee, on changes in policy, especially in relation to new drugs. It was this general support that allowed the hospital Pharmacist to stock only those drugs that were approved by the Antibiotics Committee, although it was always made clear that clinicians had the right to ignore policy if they felt that it jeopardised their patient. In fact, they seldom did this, preferring to discuss their problems with microbiologists, who, incidentally had to be available when the problems arose and not at their leisure. It is of interest that two physicians always voted against acceptance of policies since they were held to limit their clinical freedom (see Selkon, 1980), but in effect always followed recommendations. Incidentally, our surgeons commonly made no objections but were more likely to try to evade recommendations! A single psychiatrist complained when our policy substituted amoxycillin for ampicillin, but did not persist! It remains important in setting up policies to minimise what may be seen as unethical interference with a clinician's choice of drug, something that seems sometimes to be ignored in the international policies that are currently the vogue.

It will be clear that we recognised the importance of enforcing our policies. First we made available to all hospital medical staff, information on rational antibiotic use in the context of our policies, and this became a small, easily portable booklet in 1966. Many others produced similar guidelines or commented on their usefulness (Bint and Reeves, 1978; Geddes, 1977; Williams 1984; Wise, 1977). This emphasises the advice on the importance of education from colleagues such as Harold Neu in the United States (Neu and Howrey, 1975). We constantly reviewed the sources of information and education in the 1980s, including the important contribution of the pharmaceutical industry, whose representatives were encouraged to speak to members of our Antibiotics Committee before approaching other doctors (Cooke *et al*., 1980, 1985). Second, pharmacists were asked to draw major aberrations of prescribing to the attention of the laboratory doctors who would then intercede with their colleagues, a process that might have been simplified by the availability of data from computerised prescribing, which we constantly expected but never attained. The development of ward pharmacy helped this goal. Third, the microbiology laboratory was authorised to practice selective testing and reporting, a practice advocated by others (Gould, 1960; Grüneberg, 1980). For example, of the eight agents that might be tested against staphylococci only three might be routinely reported, for example. This practice was helped by the increasing sophistication of microbiology laboratory computing (Phillips, 1978) but it was later compromised by the development of a hospital market

place, in which clinicians had their own budgets and their own priorities for spending them. For some reason they never discovered the full extent of our activities on their behalf! Finally, with their strong infectious diseases tradition, physicians in the United States emphasised the importance of involving such experts in prescribing (Kunin *et al*., 1973; McGowan and Finland, 1974b, 1976) whereas in the United Kingdom we used our medically qualified clinical microbiologists for the same purpose (Gransden *et al*., 1990; Grüneberg, 1980).

2.3. Measuring compliance with policies

Despite the great efforts put into the enforcement of antibiotic policies, there was little formal indication that prescribing physicians actually followed them. Audit of policy application developed from audits of the rationality of use, for example, in the United States (Kunin, 1977a, b), where such audits became one of the bases of hospital accreditation (Counts, 1977). Other examples have already been mentioned in relation to audits of rational use.

Having appointed a pharmacist with expertise in information science specifically for the purpose, we conducted a number of prevalence surveys to assess the degree to which our policies were followed. We found that the antibiotics allowed by the policy were those actually in use. For example, in 1980, in a 1-day prevalence survey involving 120 patients receiving systemic antibiotics, we found 135 prescriptions for freely available drugs, 38 for restricted drugs (requiring the approval of a senior clinician), and only 5 for strictly restricted drugs (requiring discussion with microbiologists). However, in many cases, the drugs, especially those that were freely available, were given at the wrong time and for the wrong duration (this applied particularly to prophylaxis) and in inappropriate dosage. Findings in 1983 were similar (Cooke *et al*., 1983, 1985; Phillips and Cooke, 1985). We concluded that more education was needed—"knowing when to use an antibiotic is as important as knowing which antibiotic to choose."

3. CONCLUSIONS

Antibiotic policies had their origins in the experiences of those who introduced penicillin into clinical practice. At first, they were little more than guides to rational therapy for the individual patient, but with the increasing problem of acquired antibiotic resistance, they were extended with the intention of minimising this problem. As more and more agents reached the marketplace, an attempt was made to simplify prescribing while in more cost-concious days, economy of use was added. The more sensitive among us saw

the need not to hamper clinical freedom unduly. All this was in place by the 1970s, and in terms of concept, little has been added.

Without doubt, the application of the principles of rational antimicrobial chemotherapy has made a major contribution to human health. Unfortunately, this was at a cost, since even the most rational therapy can lead to the emergence of resistance. It seems impossible to dissect out in retrospect, the relative contributions of rational and irrational use, and to determine the overall effect of antibiotic policies. It could be argued that the proper application of policies led to the solving of many particular problems—battles have been won—but it must also be acknowledged that on a universal scale, the problem of resistance intensifies—the war is being lost. Whether this is because the concept of antibiotic policies as a means of avoiding or minimising resistance was wrong, or because the application of a fundamentally sound concept was inadequate, also seems impossible to determine in retrospect. What was once a problem for large hospitals has now spread to the whole community, and shows no sign of abating. We should now ask the question whether what we did—and continue to do—was and is, appropriate. It is to be hoped that the answer to the question will be sought by the rigorous application of sound microbiological and epidemiological science.

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