

Microbial Perturbation of Host Defences

Editors

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Preface

The great effort devoted over the years to mechanistic analyses of microbial pathogenicity and host defences has moved progressively closer to the molecular level. At the Third Beecham Colloquium we wanted to deal with some aspect of the large area of host-parasite interaction and, being anxious to focus our attentions, chose to look not at what the parasite does to the host or what the host does to the parasite, but what the parasite does to the host to stop the host doing much to the parasite.

The meeting followed the pattern of its predecessors in being held at the Medical Society of London, where a small international group talked through and around the subject almost continuously over three days. Each topic was briefly introduced by the main speaker who also provided a full paper which is published here. Most of the time was taken up by discussion which was converted into typescript with such commendable speed that at the end of each session the speakers were able to adjust the elegance of their remarks—but not allowed to write what they wished they had said. This they did so well that the editors have had to do little more than put the contributions together.

The planning of what proved to be a most enjoyable and successful meeting was marred by the death of Don Goodchild who over the years brought meetings sponsored by Beecham to a standard of excellence which was widely acclaimed. He regarded the Colloquia as the ultimate expression of his organizational skill and it was particularly sad that he did not live to enjoy the success of the third meeting. To have the main organizer die with preparations for an international meeting incomplete is a major disaster and tribute must be paid to Mrs Eileen Beirne, for many years Mr Goodchild's business associate and to his successor, Mr Ken Fergusson, who, guided by Mr Bill Burns, kept all the arrangements on course and on time to the point where only those at the centre had any inkling that anything untoward had happened. A particular debt is due to Beecham Research Laboratories who continue to sponsor the Colloquia despite the escalating cost.

We are much indebted to Miss Diana Nisbet, who constructed virtually

faultless text from manuscripts of the discussion, corrected and recorrected in places to the point of near obliteration and to Academic Press for the expeditious processing and prompt appearance of the proceedings which are so essential to publications in a rapidly moving field.

Sir Charles Stuart-Harris
Professor H. P. Lambert
Professor C. A. Mims
Professor F. W. O'Grady
Professor H. Smith
Professor J. D. Williams
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The late Mr D. Goodchild

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Professor F. W. O'Grady

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Professor J. D. Williams

Professor C. B. S. Wood

The late Mr D. Goodchild

Introduction by Sir Charles Stuart-Harris

The programme of this meeting was drawn up by the members of the Organizing Committee. In January of this year, we reached the stage of deciding that we would like to have our third colloquium on the general subject of microbial pathogenicity. But our problem was that we knew that within two days we could not possibly discuss the whole subject. We had not then narrowed the choice to one aspect, knowing that there were about four symposia planned on microbial pathogenicity and we did not then know their subject matter. Therefore I had to leave it to my colleagues to make the ultimate choice.

Infection is surely nowadays regarded as an interaction between two or more species. The outward and visible manifestations of infection are seen in the form of the pathological changes occurring in the host. Microbial species occupy the air, the sea and the soil throughout the earth in incredible numbers and varieties and some live along with the higher organisms in the form of mutual benefit.

Thus pathogenicity of microorganisms is a subject of intense medical importance and yet one which seems at times to have been relatively neglected; it would have required at least a week of meetings to discuss its various aspects. We might have chosen to discuss morphology, or genetics of pathogenic microorganisms, or the range of pathological changes in the host which they induce. Instead the Committee requested participants to discuss the subject which is at the very heart of the interaction between parasite and host, and the manner in which the parasite manipulates the defences possessed by the host against attack.

In spite of its large vocabulary, English has limitations inherent in its origins. I suggest that "attack" and "counter attack" are words which conjure up visual images. In this violent age in which we live, an attack has all the emotional connotations of battle or at least conflict. The consequences of any

conflict may be trivial or fatal. There may be destruction in various degrees, either of the host or of the organismal parasite, during the attacks of infectious disease. I find myself somewhat distressed, therefore, by the word "perturbation" in our title for it conveys no imagery to me other than a gentle disturbance. The dictionary definition of the verb "to perturb" is to throw into confusion, to disturb mentally, to agitate, to induce bewilderment. If pathogenic microorganisms do no more than disturb the peaceful existence of the host, then I suggested that we need not discuss them further.

The Committee felt that "destruction" was too violent a noun to use: it might imply that we would only be discussing matters bound to lead to fatal consequences. I am tempted to suggest that their use of the word "perturbation" in part arose from the fact that they realized that there was a terrible amount of ignorance in the subject which they devised!

From the initial abstracts that I received it was clear that some of our invited speakers had interpreted their role by discussing first and foremost the host defences and the manner in which the various forms of defence may be attacked. This struck me as an excellent way to proceed, particularly as the programme was devised on a sessional basis, roughly sub-divided according to the mechanisms of defence. Whatever our individual contributions, though, great attention was paid to the clinical relevance of our subject whenever possible.

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Some Reasons for Clinical Concern

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The microbial perturbation or disruption of host defences finds a context and a relevance against a background of some current clinical, epidemiological, immunological and genetic aspects of infectious disease. The consequences of interaction between our species and microbial pathogens are influenced by the biological characteristics of the protagonists, and by broader environmental factors. Biological factors at the site of infection are outside the scope of this chapter, but will be the content of others. This introduction deals with general factors, environmental and genetic matters and relevant changes in function and behaviour which are used to combat virulence. Apart from the innate and self-protective properties of the host, certain deliberate behavioural modifications in preventive medicine affect this interaction and may therefore be given biological and selective weight. These, together with the currently successful use of antimicrobial medication, have allowed the clinical mind to largely ignore the study of factors contributing to virulence and to perturbation as considered by this conference. Epidemiological matters, however,

continue to assist our species in keeping the balance of the contest in our favour and it must be our concern to understand them.

Historically, the situation had been much less favourable to us and early records in Great Britain reveal a very high mortality in childhood, extending beyond infancy, which was apparently even more destructive in major cities. The late Professor A. V. Neale (1964) summarized and restated much earlier information, quoting both Dr W. Farr (1805–1887, British statistician), and official records, which related to a society not yet very much affected by industrialization or by therapeutic and preventive options.

By the 1840s there was already public concern at what might be described as uncontrolled perturbation of host defences by disease. It appeared that much of the toll (Table I) was due to what is now regarded as infectious disease. To Dr Farr it seemed that infectious diseases may simply follow one another where conditions for healthy life are lacking.

TABLE I.
Births and deaths under 5 years of age.

	England and Wales	London	
	Early 20th century (1915–1924)	Mid 17th century (1730–1749)	End of 17th century (1790–1809)
Total births	927 473	315 456	386 393
Percentage dying under 5 years of age	13·8	74·5	41·3

After Neale (1964):

Neale (1964) had found that the development of concepts aimed at the control of threats to public health had begun earlier, and quotes that J. H. Rahn had proposed in 1799 that in Zurich professors should be appointed to be responsible for the following areas where a preventive influence might be brought to bear:

- Medical institutions
- Nutrition
- Housing
- Clothing
- Procreation
- Protection of mothers and infants
- Prevention and control of epidemics

Measures against animal disease

Health education

Supervision of workhouses and orphanages

These radically modern proposals were made before microbiological science had developed, although Fracastoro of Verona (1484–1553) had already proposed a microbiological theory of disease.

INFLUENCE OF ENVIRONMENTAL FACTORS

Reducing the number and extent of opportunities for host–parasite interaction has had obvious potential in preventing and ameliorating infection. The importance of water as a vehicle of infection had been recognized by Snow in 1855 and by Budd in 1956, in cholera and typhoid fever respectively. The separation of water supply from sewerage and the securing of clean water supply were necessary for the control of hitherto prevalent infection. Currently it is recognized that in parts of the underdeveloped world, gross water pollution is still common. In the rainy season, Barrell and Rowland (1980) report that in a typical Gambian village, faecal coliforms and streptococci may reach counts of 10^5 per 100 ml in drinking water. Contamination of both traditional milk substitutes, and imported dried milk feeds which require to be reconstituted with waters, is then inevitable. In contrast, in modern England and Wales, good quality water is required to yield not more than 1 microorganism per 100 ml from 50% of samples per year. Gross contamination of infant feeding preparations was frequent in Great Britain until the twentieth century, and even after water supplies were secured, contamination still occurred because of poor hygiene in food handling. In the undefended environment, the intrinsic microbial factors which enhance virulence then decimated the child population. In the early twentieth century overcrowding, which was directly related to family size, was also related to pertussis and measles mortality.

PHYSIOLOGICAL, NUTRITIONAL, AND IMMUNOLOGICAL FACTORS

The physiological reactions to infection have now been extensively studied in the context of immune response. Other physiological phenomena associated with infection include fever; while it has become common to suppress fever to achieve comfort, it is still not plain what may be the benefit to the host of febrile reaction.

The very old, very young, preterm and very ill are characteristically less able than others to mount a febrile response. Mortality in experimental infections is increased in hypothermia. Leukocyte mobility may be reduced, and penicillin and methicillin may be more active against faecal streptococci at higher temperatures (Roberts, 1979).

Complex relationships exist between nutrition and vulnerability to infection. While iron deficiency has traditionally been considered to be associated with increased risks of bacterial infection, saturation of iron bearing proteins in serum and breast milk may permit more iron to be available for microbial metabolic needs, thus encouraging microbial growth (Weinberg, 1978). Nevertheless, iron deficiency may diminish phagocyte functions (Chandra and Newberne, 1977). Nor can it be asserted that protein and calorie shortage inevitably lead to increased rates of infection in children suffering from nutritional deficits. Gross undernutrition, however, diminishes thymus dependent lymphocyte function and phagocytic killing of *Candida*, although antibody formation may continue.

The successful application of principles of antigen-specific immunity in the prevention of disease has continued to yield successful vaccines for the prevention of epidemic disease. Recently, more emphasis has been placed on determining and using the relevant microbiological antigens, rather than directing immunity against virulence or toxic factors, so that antitoxic immunity is rarely employed in the traditional sense of diphtheria or tetanus antitoxin. The delivery and acceptance of vaccine programmes involves successful administra-

TABLE II.

Newly diagnosed episodes of respiratory disease (1979). Notifications from General Practice, England and Wales
(Average weekly rate per 100 000 population).

Period	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter
Common cold	170	104.6	65.3	125.3
Influenza-like illness	148.2	64.8	41.9	70.6
Acute sinusitis	40	34.6	24.4	33.7
Sore throat/tonsillitis	153	137.1	115.9	139.9
Laryngitis and tracheitis	38.6	28.6	18.6	24.9
Acute bronchitis	110.7	76.2	54.7	81.6
Epidemic influenza	50.1	15.4	2.1	7.3
Pneumonia/pneumonitis	7.9	4.8	3.3	3.6

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tion, and husbanding of sometimes scarce resources and persuasion, through health education, if the best results are to be obtained. The management skills of prevention need to be married to the skills of immunology. It is now likely that fall in acceptance rates associated with negative publicity in relation to pertussis vaccine has now been corrected. Morley (1974) has pointed out that in certain underdeveloped societies, omitting the commitment of resources to Mantoux testing, and delivering BCG vaccine to the home, may result in a more widespread and therefore effective distribution of vaccine without causing costs to increase.

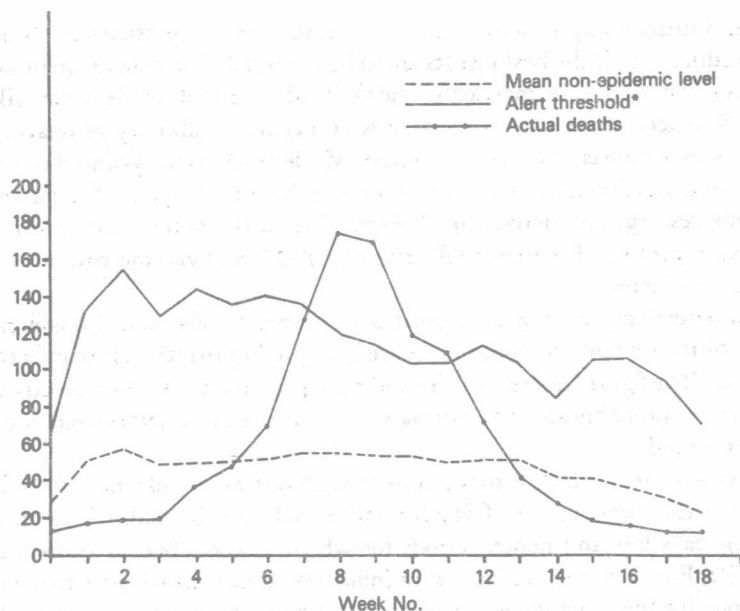
How effectively does a developed society resist infection? Considerable vulnerability remains to common place and predominantly virus infectious (Table II). The figures quoted are derived from primary health care records, and are therefore probably an underestimate, since minor cases, self treated, are not easily recorded.

It is customary in the UK to highlight the considerable influenza morbidity, for which the Department of Health and Social Security publish records of working days lost and hence periods for which sickness benefit is claimable (Table III, Fig 1). Virulence factors for influenza viruses, which are particularly hazardous for the old and very young and perhaps the fetus, are reviewed by Sweet and Smith (1980).

TABLE III.
Sickness and invalidity benefits (millions): England and Wales.

	New Periods		Days	
	All cases	Influenza	All cases	Influenza
1972-1973				
Male	7.0	1.0	250	11
Female	2.4	0.3	70	3
1974-1975				
Male	6.6	0.7	244	7
Female	2.3	0.2	66	2
1976-1977				
Male	6.7	0.8	256	5
Female	2.5	0.2	65	2

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*The alert threshold is at 1.65 standard deviations above the mean number of deaths in the corresponding week of previous non-epidemic years.

Fig. 1 Mortality from influenza: England and Wales, 1978. Reproduced with permission from the Chief Medical Officer's Report to the Secretary of State for Health and Social Security: On the State of Public Health for the year 1978, Crown Copyright.

Epidemiological aspects of bacterial infections traditionally considered to threaten developed societies have attracted less interest than formerly, and less than more recently recognized infections, such as that due to *Legionella*.

This must be seen as a consequence of the success of modern antibacterial treatment. The observed fall of case fatality for pertussis in infancy from 0.8% (1967–1968) to 0.22% (1977–1978) (CMO Report, 1978) is welcome, if little known, and may ease one aspect of the vaccine controversy.

The continuing development of various applications of intensive therapy prompts careful recording of infection occurrence and this is successfully achieved in the Public Health Laboratory Service Communicable Disease reports. In Table IV material from this source illustrates the continuing scale and severity of bloodstream infections. Particularly threatened are those in the extremes of life, including the low birth-weight infant, and those affected by trauma, surgical intervention, immunosuppression and malignancy.

Organs with special kinds of local vulnerability, e.g. the brain, or affording