# *The First Gale Memorial Lecture*

## OPPORTUNITIES AND PITFALLS OF GENERAL PRACTITIONER RESEARCH*

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A year ago today Arthur Harold Gale died at the early age of 55 and tonight we celebrate his memory by this first of a series of lectures to be delivered annually. You have done me the honour of asking me to open the series, but some of you share with me the realization that there are others better fit to undertake the task.

My contact with Gale was limited to two or three brief encounters and a little correspondence spread over a space of less than 10 years. Nevertheless, even this slight acquaintance led me to look upon him as a friend, a person to whom I could, should need arise, turn for help or advice. He produced this effect on most of those he met, inspiring, by his quiet charm, affection and confidence—a gift that was of inestimable value when in 1950 he was chosen as Director of Medical Postgraduate studies at Bristol University.

In this capacity he came in contact with general practitioners of many types and of all degrees of experience, and he was quick to grasp the opportunity afforded by the foundation in 1955 of a South-western Faculty of the newly formed College of General Practitioners. He was immediately co-opted as a member of the Council of the Faculty, and in these few short years he saw a good deal of us. General practitioners are a mixed crew, not always easy. I do not know what Gale thought of us, but the establishment of this lectureship in his memory shows what we thought of him.

A newly born creature like our faculty of the College is vulnerable and subject to many dangers and difficulties. In its earliest days before the patterns of its peculiar values, duties and relationships have become clear and fortified by traditional procedure, it depends for healthy growth upon the devotion and personality of certain individuals who take responsibility upon their own shoulders. It is they who determine whether the new infant shall integrate comfortably in the family of older societies or shall become a storm centre of faction and contention; whether it shall become a force for the encouragement of medical progress, or instead an opportunity for promoting personal ambition. Our College and our faculty have been fortunate in the personal qualities of those who have stepped

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forward to accept responsibility and in none more than Gale. His entire lack of personal ambition, his charm, tact and industry ensured a fruitful relationship between our faculty and the university. We could ill spare him at this juncture and tonight, mourning his loss, we are grateful for all he did, and shall hope to direct our development along the sane and healthy lines which he initiated.

For the thumbnail sketch that follows, I am indebted to the obituary notices in the journals and to a number of those who knew him well. Gale, the younger son of a Sheffield general practitioner, was educated at Dover College and Trinity College, Oxford. After taking his B.A. in physiology, he trained in medicine at University College Hospital, London, where he held an appointment as house officer. He took the Diploma of Public Health and soon afterwards was appointed assistant medical officer to Surrey County Council, where for three years he worked in the School Medical Service. Here his physiological bent led him to become interested in audiometry and this formed the subject of the thesis that secured him the Doctorate of Medicine of Oxford. At 32 years of age he was selected from nearly 50 applicants for the post of medical officer to the Board of Education where his natural gift for establishing good personal relationships was most serviceable.

In his writings we can detect his interest in perspective. For example, as Milroy lecturer he chose to speak of a " Century of Changes in the Mortality and Incidence in the Principal Infections of Childhood." This is frank epidemiology. He became deeply interested in poliomyelitis, and in 1947 joined the epidemiological team working with Bradley at the Ministry of Health. Three years later he went to Bristol. Despite the administrative and social demands of his new post, his epidemiological interest especially in poliomyelitis was unsubdued, and he had constantly in mind that point at which history, geography and medicine meet. He was always aware that the facts were struggling to speak to him. Something important and obvious about the epidemiology of infantile paralysis was being held up to us, and our dull eyes were missing its meaning.

Listen to this from one of his recent papers on poliomyelitis:

> I can find no evidence that there was an identifiable importation of an epidemic strain of virus at any time. It is true that ports figure largely in the early history as they did between the wars, but they were such odd ports for an importation theory. I should have thought the most likely ports for importation in the early years would be those trafficking with Scandinavia and the United States and *not* Bristol, Barrow-in-Furness or Weymouth. If the epidemic strain arrives at ports why does Leicestershire come into the picture so early ?

Why? Why? Why? His mind used to become preoccupied with such questions so that they penetrated into his daily life. He lived with them. In 1947 he told me that he was fascinated by the history

of polio in Cornwall. Nearly ten years later he was still preoccupied with the same problem. This sensitivity to problems is the hallmark of a certain type of investigator, and Cajal goes so far as to infer that you are unlikely to do useful research unless your problems get under your clothes like the itch and stay with you and worry you night and day. Gale often became abstracted and withdrawn.

The quotation from his paper continues: " I find the problem of recurrence of poliomyelitis fascinating but irritating. One feels there must be some simple and obvious explanation."

We in this faculty are going to miss this quiet, gentle, thoughtful friend and nowhere more than in our research activities. Gale would have approved the subject we are to consider tonight—the Opportunities and Pitfalls peculiar to research in general practice. He had our opportunities in mind when he wrote of a problem unanswered by a hospital investigation. " The question is difficult to answer by an experiment on outpatients."

The subject is research. Nowadays we hear on the wireless announcements such as this " The Edwin Johnson Story." Then an account of the promoters and actors of the programme, ending with " *Re*-search by Erasmus T. Bloggs." *Re*-search undoubtedly has its place in programme-construction but one wishes it could find itself a new name. In some parts of the world the process is so strongly in action—so many young people are busy digging out details of the great and the not so great in order to produce their theses on Charles Dickens, Richard Aldington or Elvis Presley, that *re*-search has become a monstrous parasite diverting precious lifeblood from useful academic activities and especially from real research.

Sad to relate *re*-search has it counterpart in medicine. There is a sort of meretricious case-mathematics that too often slides by under the flag of research. General practitioners, timid in matters of medical journalism, have not been notable offenders.

Research, the real thing, means adding in however small degree to the sum of human knowledge. How are we general practitioners placed for that?

## Opportunities

Our opportunities are enormous. Human departures from normality are our business. The populations under our care are representative samples, respectable universes even for those gentlemen so difficult to please, the statisticians. We remain for years right inside our field of observation. Even the commonest diseases hold many and important problems. What then hinders us? Where are our difficulties?

## Difficulties

First I should group together lack of consecutive time, and interruptions. We are unlikely to do good research without expending considerable time and energy. But general practice rightly conducted is an absorbing, fatiguing, whole-time occupation, more demanding perhaps than any other job. If you wish to embark on research you may need to abandon your hobbies, your exercise, your friends and even your family life in order to purchase the time that you will require. But even the highest degree of abnegation will not protect you from interruptions. You cannot immure yourself and become inaccessible to your patients. By intelligent organization you can, and you should, secure regular hours of (supposed) leisure and these will prove invaluable. But need for research activity is certain to arise outside these precious hours and you are destined to see acres of work ruined by interruption, like an oat field after a thunder-storm. Moreover, it may happen to the same piece of work again and again.

The general practitioner, unlike most other types of research worker, can seldom take up his research in the fore-part of the day. He comes to it after his legitimate duties, jaded and fatigued. Fatigue and discouragement are near kin. I think that many promising researches have been stillborn, many able and suitable general practitioners cured of their inquisitorial itch by the combined operations of interruptions and fatigue.

Remember that all this is additional to discouragement inherent in research itself. You hardly need to be reminded that research is seldom a matter of brief investigation with rich rewards. For most of us it will mean long, dull hours of routine work often terminated by disappointment because of some factor that we have overlooked or could not have foreseen when we planned the work. Do not expect sensational results from general-practitioner research. They are rare enough in full-time professional research. When you set out with enthusiasm, high courage and an idea or two, remember that your enemy No. 1 will probably be boredom, fatigue, and disappointment at an early date. The wonder is not that there are so few, but that there are so many general practitioners who brave these difficulties.

## Further Pitfalls

Second amongst the pitfalls I place the very plethora of material and the way in which it reaches us. We would like a steady manageable flow of the subjects that have excited our interest, but we must take them as they come, and this is the sort of thing that happens: ten cases of influenza appear and engage our attention, and then there are no more. We turn our attention to boils. No sooner have

we become preoccupied with a dozen boils than along comes the influenza epidemic. Our boils are laid aside whilst we struggle with the inevitable load of work. We institute some makeshift while we lie abed aching with 'flu. We totter around our patients again too soon, depressed and tired, and as the epidemic subsides we survey the sorry remnants of our investigations. Vital portions are missing. The boils are incomplete, the influenzas are incomplete, and now neither offers us cases any more and we become interested in otitis media. So we accumulate too many investigations.

Most of our research depends upon recognizing syndromes or diseases. Precise diagnosis is important. Our third pitfall is diagnostic. Even in the case of measles, although there is no difficulty in recognizing the presence of an epidemic, where research is involved the diagnosis of each case is a weighty and sometimes a difficult matter. In this way research makes the general practitioner a keener clinician. Decisions that can be awkward in measles present even greater difficulty for almost every other disease.

Laboratory and other aids are often indispensable but they always involve the practitioner in yet greater labours and from his patients' point of view, they may be irrelevant. The doctor may therefore need to secure the prior consent of his patient, and patients, not unreasonably, may fear being used as guinea-pigs. Research can thus be a hazard to a man's practice and so to his pocket.

Associated with this diagnostic difficulty is the matter of language. Our laboratory friends may not realize that a major factor in diagnosis is correct translation of the language of the patient. The patient does not say " I have pityriasis rosea," or if he does he is usually wrong. Here is an actual consultation and doubtless most of you could cap it with numerous similar episodes:—

A young man leaves his ditching and leaps into the road and stops my car by holding out his hand. " Doctor. Do ye give I a bottle for my stomach. It do bide and smertie when I do glutchie when I do bide and grubbie ? "
Translation—" It hurts when I swallow my food."
Diagnosis (later) : gastric ulcer.

I meet a carter in a remote lane and we chat. Then he says : " Doctor, I've got a hoarse."
" Oh, yes."
" I do want to get rid of 'n."
" What sort of a horse is it ? "
" 'Tis a turr'ble bad hoarse."
" Then you will find it difficult to get rid of, won't you ? "
" Oh, Ah."
" You had better see my partner. He knows more than I about horses." (He is a hunting type). " How long have you had the horse ? "
" Mebbe a fortnight."
I have a sudden thought. " Where is the horse ? "
He looks surprised, opens his mouth and points down his throat.
Translation: " I have a sore throat."

These are extreme examples, but in general practice only a fairly

long apprenticeship can minimise such sources of erroneous diagnosis.

A fourth pitfall lies in our training. It is a serious difficulty and goes much deeper than the lack of a formal course in research method. A young man abandoned a career in the classics in order to study medicine at St. Bartholomew's Hospital. Some years later he commented that while he enjoyed the work, he was astonished at and dismayed by the low standards of criticism in medicine as compared with those in classical scholarship—that so-called evidence was accepted and statements received as authoritative without adequate subjection to sceptical scrutiny. If this indictment was true—and I believe it still stands—we must look for some explanation of the relatively uncritical attitude of medicine. Good scholarship takes little account of time elapsing. If evidence is felt to be flimsy, the scholar may preserve an open mind until further evidence accrues. If none appears, he remains open-minded. He is in duty bound to remain unconvinced except upon the most solid assurances, and no one is a whit the worse for his indecision.

Now compare his situation with ours, where sick, frightened folk look to us eagerly for treatment, advice, and reassurance. The scholarly fellow who says: " It may be so and so, but the evidence is incomplete," has little to offer to the sick in body and mind. The general practitioner must give to his patient the best he can at the moment, and he must give it confidently with the assurance of established truth.

If the occasions in which there is room for doubt were few, if the areas of our ignorance were small, one might justifiably pass on to the patient the little burden of dubiety and say: " In this case we are groping in the dark. We will have to wait and see what happens." Alas, it is not so. Our ignorance remains enormous. We have no right to allow the sick man to add it to his load of malaise and anxiety and carry it for us. The good general practitioner therefore has a responsibility to be gently dogmatic with his patients. Some of us who have been patients can testify to the psychological importance of this—a doctor who *knows*, and in whose pontifications we are happy to repose our confidence. We are here in a domain more pristine than that of reason, a territory where symbols possess immense power. Some of us in our modern wisdoms run a danger of losing touch with the fears of our patients. We sneer at their dependence on the bottle of medicine, and say they must be weaned from their fanciful attachment. In situations—and they are frequent—in which we are relatively helpless, the bottle of medicine is often the most potent and most economical psychotherapy. There are signs that some patients are being weaned from the bottle—to what? In place of the simple bottle we have to

substitute the hypodermic syringe, the psychotherapist, the x-ray apparatus, the physiotherapy department. When I myself have influenza, I like my bottle.

Is it charlatanism, this deliberate partial suspension of the critical faculty in the immediate practice of medicine? I think not, although it explains the enormous success, financial and sometimes even therapeutic, of the charlatan and his advantage over more scrupulous practitioners who try to hold the precarious balance, and offer as truth only the nearest approximation possible. The attitude, nevertheless, is inclined to colour the habits of mind of the doctor, and engender a less patient approach to the search for knowledge than that of the scholar, the research worker or the laboratory man.

The difficulty is there for the consultant, but more so for the general practitioner who must shoulder the ailments mental and physical of his patients, day after day, year in, year out. The anxious mother of the sick child says: " What is wrong ? Can you put it right? " And if you say what in nine cases out of ten would be true, " I do not know," or " I think it may be so and so, but it might be that, this or the other. I think it will be self-curing but of course I cannot be certain," if you keep saying this nine times out of ten, you may satisfy your scholarly criteria but you will not be a doctor and heaven help your remaining patients. So, instead, you say: " Billy is suffering from so and so. Don't worry. He is going along normally. I will look in tomorrow." In a day or two the child is better, and Billy, his parents, and you all develop a sound affectionate relationship embodying a good opinion of yourself.

This is satisfactory because a good general practitioner knows when he is in difficulties and needs more help. But, valuable as it may be in the immediate practice of medicine, it does engender, one must confess, a readiness to accept evidence on slender grounds, and more especially so if one has oneself been involved in the matter. Perhaps I have administered a suspension of chloramphenicol to seven febrile children in succession and each has recovered with remarkable promptitude. Have I a right to refuse it to other pyrexial children? I have emphasized that we are busy people, and by the time we have devoured the more tempting portions of the useful literature of the pharmaceutical houses, we have little time and energy left for reading and reflection. Suspension of chloramphenicol offers certain advantages over suspension of judgement. We are able to say confidently to our next anxious parent: " I have some most excellent stuff for your little boy. He will be as right as rain in a couple of days." And so he is. Next time his mother comes to us with: " Can you let me have some more of that wonderful stuff for Willie? " And so we do. And we come

to believe in it all ourselves. Indeed it would be intolerable for us not to do so. And of course we may be right.

Now we wish to embark upon research in general practice. What must we do? The mind of the research worker is antithetic to what I have just been describing. He must assume a thing to be false until proven. He must be suspicious of authority and seek out its errors. Our general-practitioner research worker must therefore be schizoid. As general practitioner he must be an authoritarian, as research worker he must be a sceptic. The position is by no means easy, the more so because he must *never* allow his sceptical research self to escape beyond its proper domain. He is before all a general practitioner. In that capacity he can make the records that will form the material for the activity of his other self. But this must be a silent, stealthy research that never obtrudes.

## First Steps

When we begin, our earlier essays in research tend to be marred by a certain eager *naiveté*. We are treading new ground.

Our first lesson is that, if we would work alone, our strong suit is the common diseases. Rare diseases, for instance poliomyelitis, demand a combined operation with numerous other practitioners, and it is good to see how many such undertakings are being fostered by our College. But the common diseases by their very ubiquity ensure both that we shall have adequate provender for our enquiry, and that no hospital or consultant is likely to be able to put them into true perspective. The common ailments, then, are not only our opportunity, but in a measure our responsibility also. If we do not tackle them, who is to do so? They may remain untackled or, worse, be inadequately handled or mishandled.

Here we are, then, eager to embark upon research. What next? The first operation is usually to extract the facts, either those relevant to some hypothesis to be *assailed*, or else all the facts that will provide a balanced picture of the malady, in order to frame an hypothesis. This business of getting out the facts is a major affair, easier for us than for most other species of doctor because of our proximity to our data. Even so the difficulties are formidable. Three people successively questioning a patient may each obtain a different date for the same event. The unreliability of some witnesses should not mislead us into slovenly approximation. Our own records must be precise and accurate including if possible an account of the degree of uncertainty attaching to the record.

My own predilection is usually for the approach without preconceptions. I like trying to extract the whole pattern of a disease in my community. Like Gale, I feel that the facts are struggling to speak to us. The more facts there are, rightly analysed, the clearer

becomes the pattern—or so it should, because the pattern is bound to contain the information we are seeking.

" Got anything to tell me ? " said the Commissioner.
" No sir, I can't say I have. The soup's thickening nicely, which is as far as I'm prepared to go at the moment," replied Chief Inspector Hemingway.
" You seem pleased ! " said the Commissioner.
" I am," admitted Hemingway. " In my experience, Sir, the thicker it gets, the quicker you'll solve it." (Heyer, G., 1956).

Sometimes it takes years to thicken our soup sufficiently.

I would draw your attention to another aspect of this business of obtaining the record. Essential, laborious, sometimes interesting, but it is not, by itself, a piece of research. *Re*-search, yes, but to transform it into research it needs to be completed by discovering the inferences that may be drawn therefrom, or by using the material to support or destroy a current hypothesis.

Do not misunderstand me. One must not undervalue the tremendous business of recording the behaviour of disease, and rendering down the mass of raw fodder into the appropriate rates and incidences. These are to the epidemiologist what the bottles of reagents are to the chemical laboratory, and are often well worth publishing because they may otherwise be lost to others. We, therefore, who undertake to extract some data from our practices should realize that others may also use our material for their own purposes. Let us see to it that all necessary information is included. Just as the laboratory worker need not himself have manufactured his reagents, so we too may learn to use the figures supplied by others, and to extract figures from our own records and to present them in a useful form. At present the epidemiologist's " laboratory " is poorly stocked with such " reagents ". Moreover the lability of some viruses calls for a continuing record to keep pace with their genetic changes.

Sometimes we are devastated by a critic who says: " Ah yes, but what about all the symptomless cases? Many of those affected by this agent are without any symptoms of disease."

Now, we are concerned with the causes of *disease*, and if, say, of 100 persons infected with virus X only three produce symptoms, then the correct conclusion is that virus X is *not* the causal agent of that disease. The correct statement is that the disease is caused by some agent acting on persons harbouring the otherwise harmless virus X. Apply this reasoning to poliomyelitis and what do we get? Something of this sort:

" Acute anterior poliomyelitis is caused by some factor operating in a small proportion of persons harbouring the normally harmless so-called poliovirus." How urgent it becomes, does it not, to

discover the unknown factor? Throughout investigations of this sort the laboratory should be our handmaiden, not our master.

My own preference for the approach without an hypothesis, a method frowned upon by many experienced research workers, stems from some early experiences. After a few essays in research from which I think the curtain of obscurity is best not withdrawn, I chose to investigate measles, thinking that here was an academic exercise, a disease so well worked out that we should be undisturbed by any discoveries and could concentrate on techniques. What was the result? So soon as we began to obtain precision and accuracy, the emerging patterns of the disease in our community fairly shouted exciting new knowledge at us.

Technique is of the first importance. Every turn and twist of a disease in the community is eloquent of the nature and behaviour of the causal agent and it is only our bungling that conceals the messages.

We shall achieve little unless we have some basic knowledge of our practice. The age and sex of all patients should have been ascertained so that the incidence of diseases can be calculated as rates in specific age-sex groups in addition to the general rate for the population. The record should be adjusted continuously for additions and withdrawals and a fresh census should be made now and again to check accuracy. For this purpose staffing problems become important.

What can we hope to discover? I have said that it is unlikely to be anything spectacular. Nevertheless we are sometimes blind to our opportunities.

## Examples

I was asked to illustrate this lecture by an account of some work in progress on the common cold. I have decided against this because it is controversial and suits a discussion better than a lecture, and because I have already spoken of it at a College meeting. Instead I shall seek to show you how well a general practitioner is placed to investigate the intimate biology of human parasitism.

Suppose you wish to study a certain parasite, what sort of information would you seek? You would require to know the duration of its reproductive cycle, the time in the host-parasite relationship at which migration to a fresh host occurs, the duration of this period of infectiousness, and the degree of infectiousness.

Let us attempt to obtain such information from the routine events of the practice. Let us take parasites like those of measles, chickenpox, or mumps—so small they cannot be seen by the orthodox microscope, so eclectic that they have only very recently been grown in the laboratory. But we, without recourse to the laboratory, can uncover their secret lives because our patients are their natural hosts.

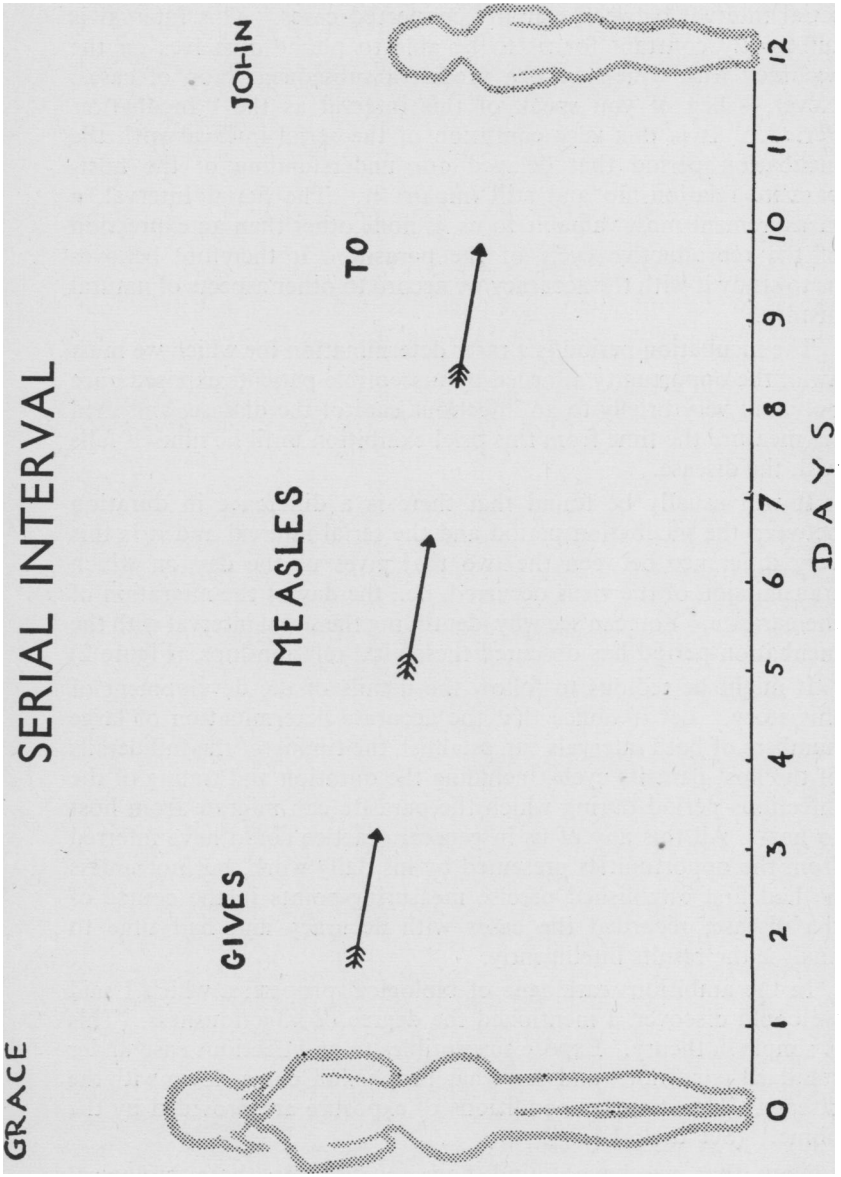


FIGURE 1. Serial Interval.

## Virus Natural History

Take first the duration of the reproductive cycle. (Figure 1) We all know that for each of these diseases there is a fairly constant serial interval between causally connected cases. This interval is sufficiently constant for us to be able to plume ourselves on the accuracy with which we can predict a subsequent crop of cases. Never, I beg of you speak of this interval as the "Incubation Period." It is this very confusion of the serial interval with the incubation period that delayed our understanding of the host-parasite relationship and still impairs it. The Serial Interval, a measurement most valuable to us, is none other than an expression of the reproductive cycle of the parasite. It therefore behoves us to study it with the accuracy we accord to other aspects of natural history.

The incubation period is a rarer determination for which we must await the opportunity afforded by susceptible patients exposed once only and very briefly to an infectious case of the disease, and then we measure the time from this brief exhibition until he himself falls with the disease.

It will usually be found that there is a difference in duration between the incubation period and the serial interval and it is this very difference between the two that gives us the day on which transmission of the virus occurred, i.e., the day of the migration of the parasite. You can see why identifying the serial interval with the incubation period has obscured these vital relationships. (Figure 2)

It might be tedious to follow the details of the development of this story. Let it suffice that the accurate determination of large numbers of both intervals can establish the timing of the full details of the host-parasite cycle, including the duration and timing of the infectious period during which the parasite can migrate from host to host. All this any of us in general practice could have inferred from the opportunities presented by his daily work, but not unless he had first established precise measuring-points in the course of the disease, recorded the cases with accuracy and had time to analyse the results intelligently.

In the ambitious catalogue of biological properties which I said we could discover, I mentioned the degree of infectiousness. This is simple in theory. Expose susceptibles to an infectious case under standard conditions and see what proportion come down with the disease. The standard conditions of exposure are provided by the home. (See table I.)

Now that we have found how to discover these biological properties—reproductive cycle, infectiousness, etc.—for measles, we can equally obtain them for mumps, chickenpox, and other

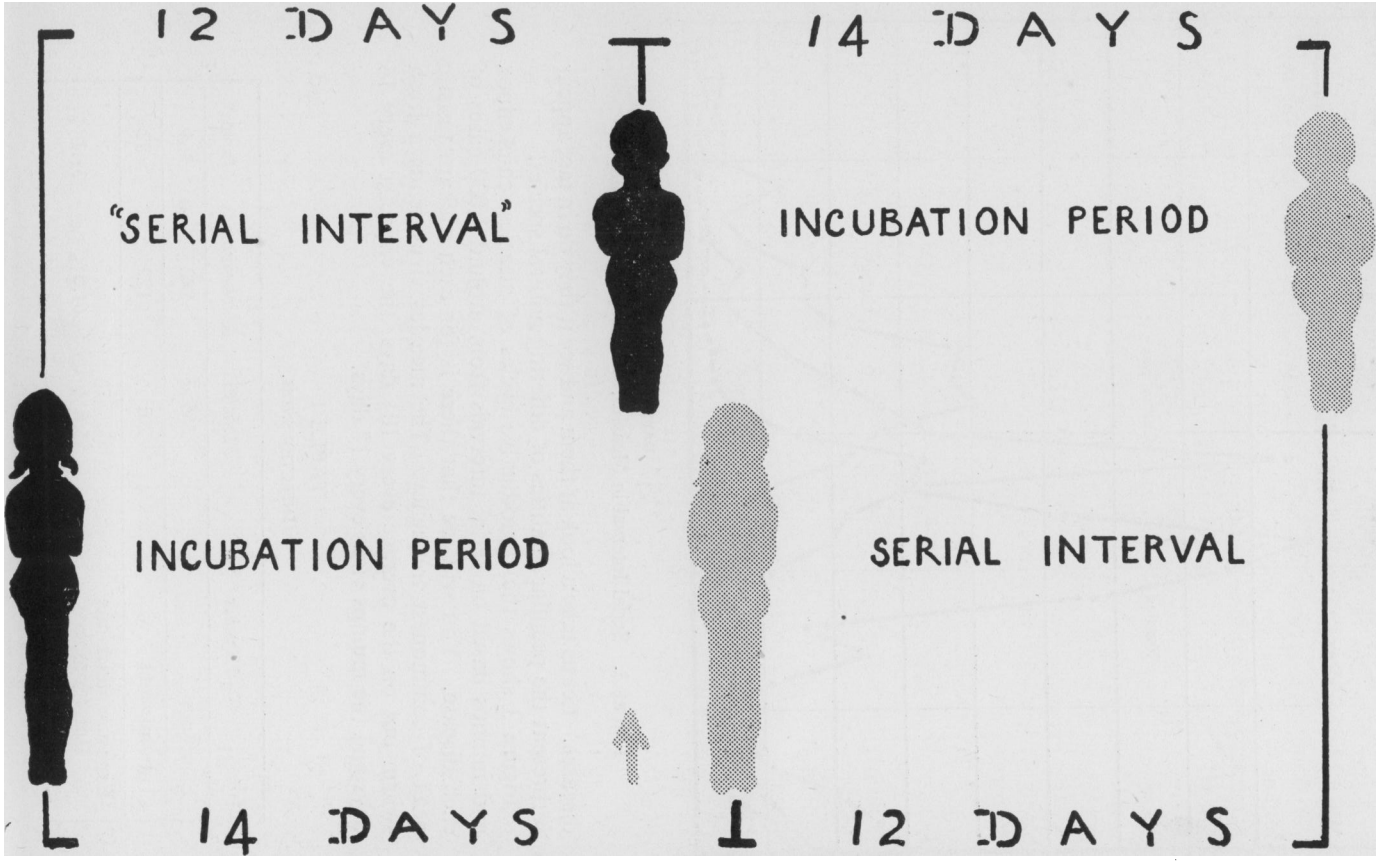


FIGURE 2. Behind the Scenes of the Serial Interval.

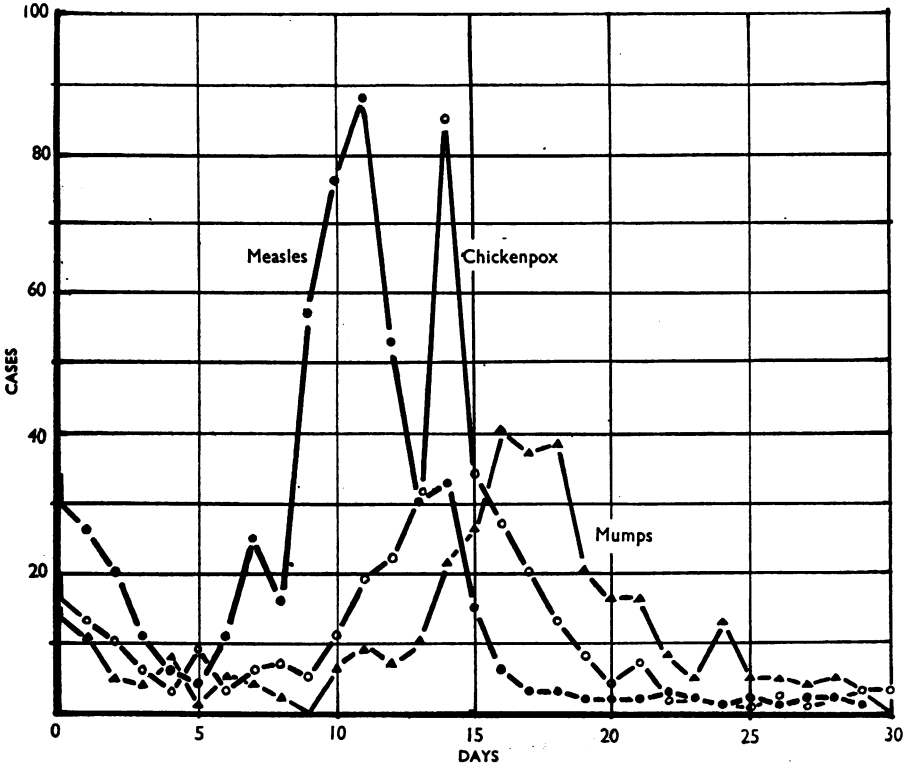


FIGURE 3. Serial Interval in Measles, Chickenpox and Mumps.

diseases. Let us take a look at them and see if they do in fact appear to present the peculiar qualities of differing natural species.

Figure 3 shows the reproductive cycles of measles, chickenpox and mumps based on serial intervals from around 1,000 cases of each disease. You will see that there is for each a characteristic peak of commonest frequency. The measles virus sends a fresh swarm out on the average every 10½ days, the varicella every 14 days and the mumps virus every 17 days.

TABLE I

INFECTIOUSNESS.

| 0—15 *years* | *Measles* | *Chickenpox* | *Mumps* |
|---|---|---|---|
| Exposures .. .. .. | 266 | 282 | 264 |
| Transmissions .. .. .. | 201 | 172 | 82 |
| Exposure attack-rate (Infectiousness) .. .. .. | 75.6% | 61.0% | 31.1% |

Table I shows the infectiousness in the home of these three diseases based on the exposure attack rate. Here you will notice that measles has an infectiousness of about 75 per cent, chickenpox about 60 per cent and mumps about 30 per cent. Do you notice the inverse correlation between the duration of the reproductive cycle and the degree of infectiousness? The shorter the cycle the more infectious the virus. Now a disease that is more infectious and has a shorter cycle ought on the average to attack at an earlier age. Let us see if this is so.

Figure 4 shows the mean age of attack of these same cases. As we had predicted measles attacked at the youngest age, 5½ years,

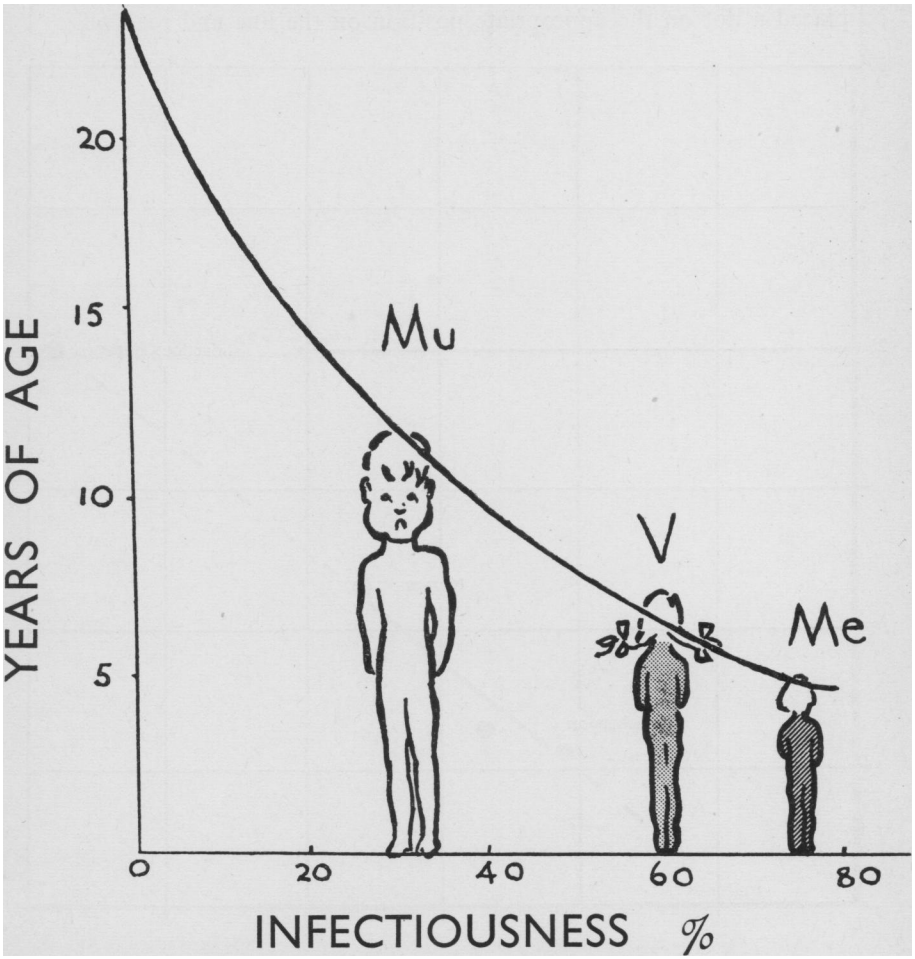


FIGURE 4. Relationship between Infectiousness and Age of Attack.

and chickenpox at $6\frac{1}{2}$ years and mumps at $11\frac{1}{2}$ years. This provides corroboration of the correctness of the previous results. It also allows us to play an interesting game.

## A Periodic Table?

In figure 5 I have plotted the mean age of attack on the vertical line against the serial interval on the horizontal line. Measles with its cycle of 10 days is seen attacking at the mean age of $5\frac{1}{2}$ years, chickenpox with its cycle of 14 days attacking at $6\frac{1}{2}$ years, and mumps with its longer cycle attacking at a mean age of $11\frac{1}{2}$ years. Let us assume that these points fall along a line and prolong it upwards. Now we extracted the mean age of attack in our patients with infective hepatitis and found it to be 20 years. We then placed a dot on the appropriate position on the line and read off

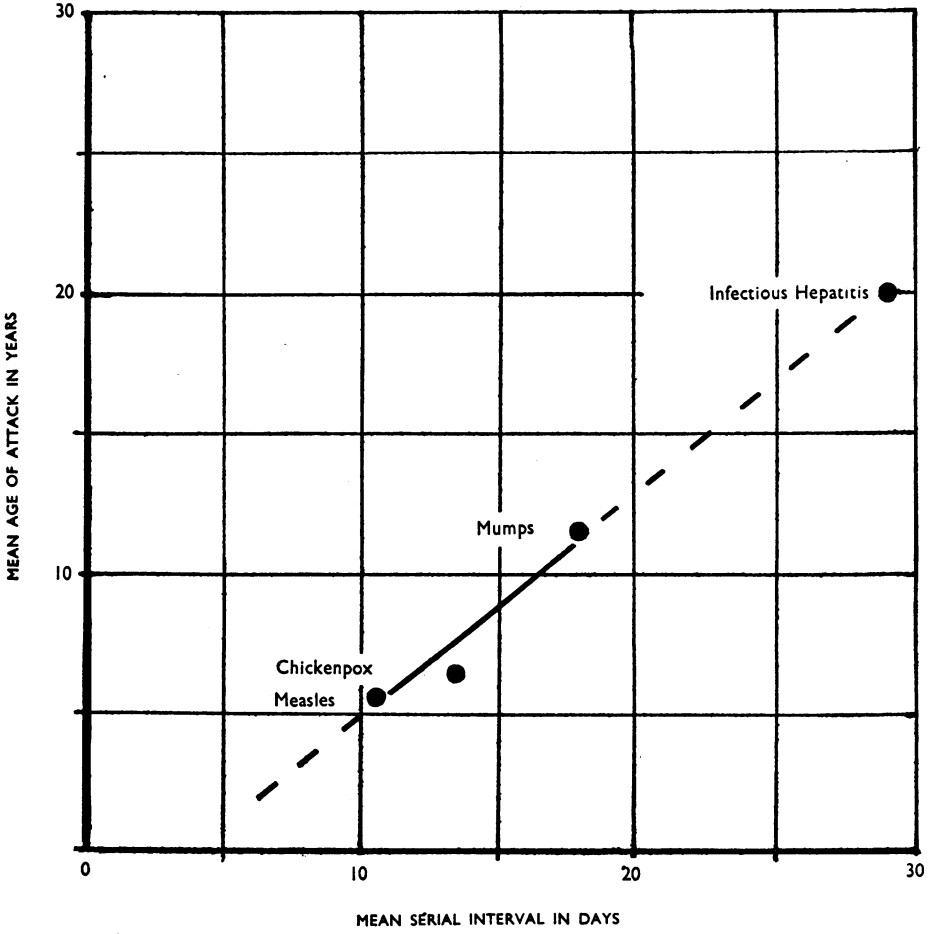


FIGURE 5. A Periodic Table of Diseases ?

what this extrapolation gave as the serial interval for infective hepatitis, and found that it gave us the figure of 29 days—not far off the true figure.

Is there, perhaps, for diseases caused by viruses of this sort a periodic table? If so, on what does it depend, what diseases are included and where does it stop? You will remember that infectiousness declined as the reproductive cycle increased in duration. The possibilities are intriguing but you must bear in mind that it is probably no more than a coincidence.

## Uses

At this point you may feel inclined to say: " Interesting this may be as natural history, but of what use is it? Has it any practical application? "

TABLE II

DEMONSTRATION OF TRANSPLACENTAL IMMUNITY IN MEASLES BY THE SECONDARY ATTACK-RATE IN THE HOME.

| *Age-group (years)* | *Secondary attack-rate* | |
|---|---|---|
| | *Providence, U.S.A.*, 1929-34 (*Wilson* et al. 1939) | *Cirencester* 1947-51 |
| Less than 1 .. .. | 40.6 | 40.0 |
| Less than 15 .. .. | 81.1 | 80.1 |
| 15 or more .. .. | 16.7 | 16.3 |

In reply may I give a few illustrations. It is useful to know how much immunity is transmitted from mother to infant. The immunity can be quite simply measured by the diminution in apparent infectiousness. In table II you can see that the infectiousness of measles in all infants under one year was 40 per cent as compared with 80 per cent for older children. These were our Cirencester figures made comparable with some figures from Providence, U.S.A. gathered many years earlier by Wilson and his colleagues (1939). Evidently there was little difference between our measles and theirs despite the difference in date and geography—another indication that we are dealing with biological constants.

Here is another illustration. It is sometimes said that there is a seasonal change in infectiousness of viruses and that sudden epidemics of, for example, measles, are due to heightened infectiousness. We decided to try to test this hypothesis. In the outbreaks with which we had to deal the greatest prevalence of measles was in July and the months on either side of it. Was this because the measles virus became during these months temporarily more infectious?

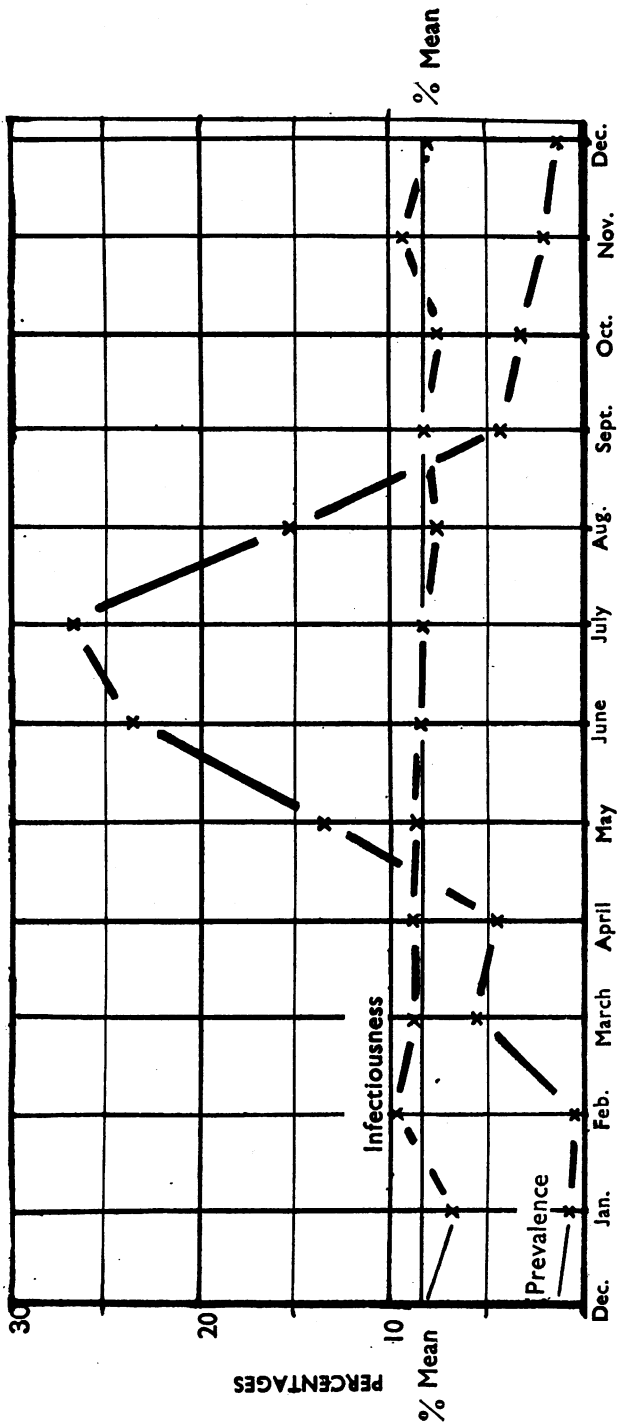


FIGURE 6.

Measles 1947—1951. Percentage Seasonal Prevalence and Infectiousness.

Figure 6 shows the prevalence and the infectiousness, based on precisely the same cases, as a percentage of the mean value of each. There appears to be no change in infectiousness to account for the increased summer prevalence and we clearly have to look for some other explanation, probably in the behaviour of the host species. It has been pointed out that quite small variations in infectiousness might be sufficient to produce very big results. In any case, here is a method for investigating the problem, and here also is a sensitive method for watching for virus mutations. If a virus mutates it will differ from its progenitors and the differences will be reflected in just these bionomics that we have been discussing. If we had possessed this sort of information for german measles, we could have stated categorically whether the pandemic of 1938—1941 was " ordinary german measles," a new disease, or a mutant with some degree of cross immunity. Alas, we do not possess the information even for the pandemic.

## The Zoster-Varicella Problem

Here is another problem which for two generations has exercised many minds. Zoster will often give rise in contacts, especially children, to a disease clinically indistinguishable from chickenpox. Is this in fact ordinary chickenpox, or is it a similar disease due to an unrelated virus, or is it perhaps due to a mutant of the chickenpox virus retaining some immunological affinities with its parent? That sounds like a laboratory problem, does it not? However, until very recently the viruses of chickenpox and zoster could not be cultivated in the laboratory and no experimental animal but man was susceptible. So man it had to be, and, as the natural host, he is the best for the purpose.

We already possessed, as you have seen, some basic knowledge about ordinary chickenpox. The solution of the problem seemed to require information on the bionomics of what I will call Z-varicella, the disease caught from cases of zoster. If the reproductive cycle and infectiousness differed considerably in the two sorts of varicella, it would be unlikely that the viruses were identical. We had the good fortune to be informed of an outbreak of Z-varicella in Shetland. We therefore decided to take a busman's holiday there. I wish I had time to tell you more about that. Here are some of the results.

From table III you will see that the reproductive cycles of the viruses of ordinary chickenpox in Cirencester, ordinary chickenpox in Yell and Z-varicella in Yell were similar. Table IV shows that the infectiousness of ordinary chickenpox in Cirencester, ordinary chickenpox in Yell and Z-varicella in Yell were closely similar.

TABLE III

DURATION OF REPRODUCTIVE CYCLE.

| | *Mean cycle (days)* |
|---|---|
| Ordinary varicella in Cirencester area (178 intervals) | 14.0 |
| Ordinary varicella in Yell .. .. (32 intervals) | 14.0 |
| Z-varicella in Yell .. .. .. (14 intervals) | 15.1 |
| Z-varicella in Yell (5 generations of virus in 69 days) | 13.8 |

TABLE IV

INFECTIOUSNESS AMONGST CHICKENPOX SUSCEPTIBLES.

| | *Exposures* | *Transmissions* | *Rate %* |
|---|---|---|---|
| Ordinary varicella in Cirencester | 282 | 172 | 61.0 |
| Ordinary varicella in Yell .. .. | 77 | 45 | 58.4 |
| Z-varicella in Yell .. .. .. | 30 | 19 | 63.3 |

These findings made it possible that the viruses were identical or related but they did not prove it. How were we to decide?

In the laboratory you would take some experimental animals, find out what proportion would on challenge take each disease, find out how much protection an attack afforded against subsequent challenge by the same virus and, finally, find out how much protection an attack by one virus left against subsequent challenge by the other—the so-called cross-protection test.

That is precisely what we did. We managed to find sufficient households in which persons who had had Z-varicella were subsequently challenged by a case of ordinary varicella and vice versa. We knew from the previous studies what proportion should come down with each disease were there no cross-protection. What happened?

In table V you will find 28 people, known to have had ordinary chickenpox, exposed in their homes to infectious cases of Z-varicella. If no cross-protection is conferred we should expect a 63 per cent attack rate, i.e., 18 persons to catch the disease. In fact none caught it.

TABLE V

RESPONSE TO Z-VARICELLA VIRUS OF THOSE WHO HAVE HAD ORDINARY CHICKENPOX

| | | | | |
|---|---|---|---|---|
| Exposures 28 | Expected transmissions | .. | 18 | Rate 63.3% |
| | Actual transmissions | .. | 0 | Rate 0 |

TABLE VI

RESPONSE TO THE VIRUS OF ORDINARY CHICKENPOX OF THOSE WHO HAVE HAD Z-VARICELLA.

| | | | | |
|---|---|---|---|---|
| Exposures 13 | Expected transmissions | .. | 8 | Rate 61.0% |
| | Actual transmissions | .. | 0 | Rate 0 |

Table VI shows the opposite challenge. In this case there are 13 people, who had had attacks of Z-varicella, subsequently exposed to risk in the home with infectious cases of ordinary chickenpox. If they were unprotected by their attack of Z-varicella 61 per cent of them, i.e., 8 should have come down with chickenpox. In fact none did.

Although the numbers are small the result is clear-cut evidence of solid cross-protection, and it must be considered that there is a very high probability that the virus excreted by cases of zoster and causing a chickenpox-like disease in contacts is ordinary chickenpox virus. As a matter of fact, evidence in support of this conclusion was coming in whilst this work in Shetland was going on. The viruses of chickenpox and zoster were at last successfully grown on tissue culture in the United States, and by a most elegant technique using fluorescent antibody, it was shown that in the laboratory too there is complete cross-protection.

Here I must end. I have tried to give you an account of some of the sort of work which the man we are commemorating tonight was attempting to promote during his association with our College.

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Tables I, II, III, IV, V, and VI and figure 6 are printed by courtesy of the Editor of the *Lancet*.