CURRENT APPLICATIONS

OF

EPIDEMIOLOGICAL METHODS

EDITED BY

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by

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and

THE INTERNATIONAL CORRESPONDING CLUB

Preface

The International Corresponding Club, now to be renamed the International Epidemiological Club, which came into being in order to facilitate communication among medical men and women engaged in teaching and research in social and preventive medicine, held its first International Seminar in Noordwijk, Holland, in July 1957. On the last morning of the meeting we were invited to the Netherlands Institute for Preventive Medicine, where we met most of the senior staff members and saw something of the many activities of the Institute. It seemed to our hosts that they would gain a better understanding of the new trends in epidemiology if some members of the International Corresponding Club could spend a few days in discussions with them and some of their Dutch colleagues on current work in the broad field of social medicine. It was therefore arranged that the Executive Committee should hold its 1958 meeting at the Netherlands Institute for Preventive Medicine when the opportunity would be taken to participate with our Dutch colleagues and a few additional invited speakers in a two-day symposium on "Current Applications of Epidemiological Methods." This meeting was a great success and so it was felt that the principal contributions should be published as a small book, which might help to stimulate interest in the uses of epidemiology in the advancement of social and preventive medicine. The onerous task of collecting and editing these contributions has been undertaken by Drs. Buma and Sunier, the Acting Directors of N.I.P.G., and we are most grateful to them not only for preparing this useful manual but also for being our charming and generous hosts during our stay in Leyden.

Robert Cruickshank
Chairman of Executive Committee,
International Corresponding Club

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OPENING SPEECH

PROF. DR. P. MUNTENDAM, Director-General of Public Health (Netherlands):

It was on the 26th of May 1958 that I was among the audience of Milton Eisenhower, a brother of the President of the U.S.A. and he himself President of Johns Hopkins University in Baltimore. Milton Eisenhower addressed the tenth anniversary commemorative session of the W.H.O. in Convention Hall, Minneapolis. He made a most important statement, namely he announced that the President of the U.S.A. was going to request U.S. Congress to vote a supplementary estimate amounting to 300,000 dollars, which amount was to be made available to W.H.O. for research, in which connection particular mention was made of cardiovascular diseases and cancer. A draft resolution was made by the American delegation in the Assembly in order to give the Director-General of W.H.O. a guiding-line as to how this amount ought to be spent. In my opinion the original draft shown to me was not concrete enough. I had the pleasure to convince my American friends Burney, van Zile Hyde and Hilleboe that in research priority should be given to epidemiology, particularly for studying the diseases explicitly mentioned by Milton Eisenhower. And thus it happened that epidemiology was inserted in the resolution.

Well over two months ago I delivered a lecture for the Netherlands Society of Chest Physicians on the Influence of the Social Surroundings on the Manifestation and Course of Tuberculosis. Speaking about the correlation between nutrition and health condition, I stated that there are three lines of approach to this question, viz. epidemiological research, laboratory research and clinical research. Although none of these methodologies can be studied disconnected from the other two, I was of opinion, specifically in my function of Director-General of Public Health, that priority should be given to epidemiology. I may be permitted to quote my own words:

"As Public Health Administrator we place epidemiology first, as we are of opinion that a modern department of public health, run by the municipality, the province or the State, should have at its disposal a division of epidemiology, charged with the study whether there is a causal connection between the influences which the community may have on the spreading of diseases in order to provide the best possible guarantees for an effective prevention and a rational control of these diseases."

It is very gratifying for me to welcome Dr. Lester Breslow in our midst. I was among his audience in Atlantic City, November 1956 where he presented his most interesting paper on the California Health Survey. We greatly regretted, that Dr. Breslow was unable to attend the symposium in Amsterdam in 1957, but after that I still had the opportunity to correspond with him on his Health Survey, which may form an important contribution towards the epidemiology of chronic diseases.

Morris told me when we met in Copenhagen last April that he would be unable to attend this Symposium. In Copenhagen we once more had the opportunity to emphasize the importance of epidemiology in an advisory group on cardiovascular diseases of the World Health Organization.

Three weeks ago I had the opportunity in Minneapolis to discuss with Ancel Keys the possibility of extending his epidemiological research on the correlation between nutrition and atherosclerosis to the Netherlands. My University department, located in this building, is also greatly interested in this research.

Dr. Salk was a member of the American delegation in Minneapolis and I once more had the opportunity to discuss with him numerous epidemiologic aspects of poliomyelitis in detail. I mention this lest you should think that I exclusively associate the conception of epidemiology with chronic diseases.

So one sees how much significance I attach to epidemiology, both from a scientific point of view and from the point of view of Public Health policy.

WELCOME TO THE PARTICIPANTS

DR. J. T. BUMA, Acting Director of the Netherlands Institute for Preventive Medicine:

Before I give my remarks on the concept of epidemiology, I should like to say some personal words on behalf of the directorate of this Institute and of the Dutch participants of this Symposium.

It is for us all an honour and a great pleasure to welcome in our midst the Executive Committee of the International Corresponding Club for Social and Preventive Medicine and our other guests from abroad.

We are here to discuss theoretical questions and more practical ones. The theoretical aspect of our discussion will be concerned with the classic and with the more modern concept of epidemiology; the more practical field of discussion will deal with their application in the fields of social and clinical medicine, their functions in our endeavour to come to a better understanding of the natural history of disease, more complete clinical pictures and last but not least to realise a better hold on actual public health problems.

Dr. Sunier and I were very happy, when you asked us to give our support to the organization of this symposium, because we are deeply convinced that the attack on some of the biggest present day public health problems is seriously hampered by technological impediments, which in our opinion can be attributed to a large extent to inadequacy of the methodological basis of social and possibly also of clinical medicine in our days.

If what I said in my lecture is true, namely that the scientific basis of social and preventive medicine is still weak, much work of the kind we propose to perform during this symposium lies ahead.

Both Sunier and I wish to express our hopes that this symposium may contribute, not only to the reciprocal understanding of social medical research workers in the countries represented here, but also to a better foundation of social medicine as a science.

On the concept of epidemiology

DR. J. T. BUMA
Acting Director
of the Netherlands Institute for
Preventive Medicine, Leyden

Epidemiology is an instrument, which like any scientific method, must serve us to measure, to bring under intellectual control, or indirectly to handle an aspect of reality in the scientific and practical sense.

Let us try to consider the functions of epidemiology against the background of quantitative and qualitative changes in morbidity in Western countries like ours. For a clear estimation of our position we have to go back a few steps in medical history.

As we all know, the discoveries of the specific causes of the infectious diseases particularly led towards the big successes of clinical and preventive medicine, and as a result of these, towards a complete revolution, not only in mortality and morbidity patterns, but also in the composition of whole populations.

Apart from infectious epidemics, intoxications and deficiency diseases came under control.

In this phase of medical history, at the end of the 19th and the beginning of the 20th century, clinical medicine, and epidemiology also, considered the specific symptom, of the specific pathogenic factor, of the specific process, the mainstay for therapeutic, preventive and scientific policy.

The discovery that behind the wide variety of symptoms and complaints that every syndrome displays, specific processes can be brought to light, led to sufficient possibilities of identification of a great number of syndromes in spite of the diversity in the clinical pictures. It was these clinical entities that offered the possibilities for the development of epidemiological studies, based on morbidity-statistics and for a policy of eradication of a number of epidemic diseases.

In their enthusiasm as consequence of these discoveries, the scientists tended to overlook the fact that for the occurrence of illness more than one external factor alone is indispensable, as pointed out by professor Grundy[1]: "Even for the few diseases where a *necessary*, specific disease-provoking agent – quite a different thing from a cause – has been identified, it is rarely a *sufficient* factor and never the *sole* factor; often it is not the most important factor in the practical sense!"

Although however scientifically speaking the qualification of the specific factor as "*the* cause of illness" is wrong, in this phase of medical history epidemiology on the above mentioned base became a valuable instrument in the battle against infectious disease, and until the second world war the term was only used in connection with illness in which a specific agent was present.

After the last war, and mainly in Anglo-Saxon literature the term gradually came in use associated with non bacteriological or virological diseases; epidemiology developed into the science of natural history of the total complex of relations, not only between the micro-organism and its host but also between man and his environment.

Not long ago, Prof. J. J. Van Loghem[2], teacher in our country of two generations of bacteriologists and hygienists, raised the question if the extension of the use to non infectious diseases is to be regarded as legitimate. I cannot see any intrinsic drawback or objection against the extension of the use of the term, but on this point of course opinions may differ.

We have found Prof. A. Ch. Ruys willing to deliver the first contribution for this symposium and are very grateful for her readiness. It will be interesting to learn about her opinion on the just mentioned discussion point, as she is both pupil and successor of Prof. Van Loghem.

To our opinion epidemiology simply means the logic, the science, dealing with the laws of distribution of a phenomenon (e.g. illness) in a population, whatever the nature of the phenomenon under consideration may be.

Let us now consider in brief the main conditions, indispensable for epidemiologic studies.

In the first place agreement must be reached between epidemiologists as regards the fields to be covered, the distributions to be studied, the countable units to be taken into account. In case of illness due to specific causes this question seems a simple one. But even so much discussion remains possible about the countable unit, to which the illness has to be reduced for statistical use.

We all know the discussion about the question "What is to be regarded as a reportable case of tuberculosis." When reading the literature about these discussions one is struck by a remarkable fact, i.e. that the presence of the specific agent alone is not sufficient for the decision: tuberculosis or no tuberculosis, for the decision whether a certain case fits as "Unit of Observation" in epidemiological enquiries.

This "Unit of Observation" agreement, this countable unit (this "case of tuberculosis") is not sufficiently limited and defined by the presence of a tuberculous process alone.

All boundaries between infection and illness are arbitrary ones.

In our country as dividing-line is chosen the necessity of treatment. I need not tell you how defective such a background is as a base for the second condition, necessary for epidemiological studies: morbidity data.

This difficulty in the process of discrimination between sick and healthy individuals is still more difficult in regard to diseases which cannot be attributed to specific causes, like in the case of neurosis, alcoholism, and so on.

The less specific pathognomonic symptoms are present in a form of disease, the greater the difficulties that arise in reaching agreement about the question of the reportable cases of the disease. One of the main problems of the modern epidemiological approach of non-infectious diseases lies in my opinion in quantitative and qualitative descriptive difficulties.

The contribution by Sunier will deal with this problem. I found an illustration in a recent *W.H.O.-Press* [3]:

> Alcoholism is now considered in many countries as a top public health problem, and as such it is investigated by the World Health Organization. It is believed however that statistics cannot give a true picture of the extent of this problem. For one thing, there are no data on the incidence of alcoholism – that is, on the number of cases. Even the number of deaths attributed to alcoholism or cirrhosis of the liver cannot be held to give the total mortality from this cause because alcoholism is either the direct cause or a contributing factor in many deaths which appear under various statistical chapters, for instance accidents, suicides, homicides, as well as several diseases.

Before continuing our enquiries into the functions of epidemiology, allow me to comment on the changing morbidity patterns in our societies.

According as less and less young people die of *infectious diseases*, more older people remain to develop *degenerative* and other diseases of wear and tear, associated with old age.

Parallel to this development chronic diseases and invalidity lay an ever increasing burden upon those, responsible for health care of individuals and populations. It is really a burden, because it contains new elements.

As the average patient becomes older, and as specific aspects of illness become less important, our therapeutic possibilities grow more and more deficient, or even absent. Parallel to this rehabilitation becomes relatively more important. The physician however, trained in curative methods that enable him to handle defects in health (illness) of the individual, is in the rehabilitation situation confronted with something totally new, namely the necessity to develop methods that must enable him to handle aspects of the human totality, such in spite of existing defects.

This is one reason for the discovery in the last decades that knowledge of the pathogenic

process alone is in many cases not enough to understand the development of illness, and especially to treat (rehabilitate) patients in a satisfactory way.

Diagnosis ought gradually to become more functional, measuring the limitations of the fields of (normal) mental and physical functional response.

In psychiatry, especially in our country, the insight came, that it is more useful to cultivate healthy aspects of a defective personality than to accept the defect as incurable. Mental hospitals, together with after-care-services, are transforming into rehabilitation centres.

Parallel to this development the epidemiology of health is as important as the epidemiology of illness. Only too slowly the general hospitals follow this development into centres of rehabilitation.

Two hundred years ago in this town Boerhaave started to collect patients in the few beds he had at his disposal; he propagated the necessity of underbuilding clinical medicine with the whole spectrum of scientific methods that were at hand. Thus he developed the principles of clinical, descriptive medicine which led to the description of almost every syndrome.

Now exactly 100 years ago Claude Bernard [4] began his investigations and *annotations*, leading to his concept, published only a few years ago, of "the principles of experimental medicine."

These two complementary principles, clinical description and laboratory experiment, led to our extensive knowledge of pathogenic processes.

Modern medical science is faced with the necessity to assimilate the idea that knowledge of the pathologic process does not suffice to define illness, this includes that knowledge about the external and internal conditions under which illness develops, is just as essential as knowledge of the specific or typical process. Ecological principles need a more central place in medical thinking and policy.

Every human being lives continuously under all possible forms of stress, be it pathogenic agents like tubercle bacillae, polio virus strains, or the more normal stresses of human life. Life, as an English philosopher has said, is the continuous adjustment of internal relations to external relations; the human individual is a variable, living in an ever changing field of forces. In the case of illness the internal functional apparatus gives signs of insufficiency and according to the modern concept, illness is no longer a question of presence of a pathogenic process only, it is an insufficient adaptation process.

Descriptive and experimental medicine are faced with a new task, namely determining and measuring the factors working in the normal conditions of everyday life. The development of methods to determine and measure those factors is the task of epidemiology according to our present day views.

In these factor-analysing enquiries, studies in pathology do not or not principally distinguish themselves from normal "conflictuology" (logic of conflicts in all-day-life).

When Prof. Ruys talks about silent epidemics, and Sunier will occupy himself with neurotic symptoms, developing under stress situations, it must not be easy for them to decide as to whether they are talking about sick or healthy people. As Sunier once formulated: "the less we know about an individual, the more we will be inclined to declare him sound."

In an epidemic in the classic sense some form of microbial life shows itself in an explosive way. But although we know much about the specific aspects of epidemics, many of the aspecific factors and conditions remain in the dark. Our knowledge about the external conditions that are responsible for the development of diseases like tuberculosis or polio-

myelitis is extremely small, if compared with the insight in the internal processes (Dubos [5]). Our predecessors talked about the complex as the "genius epidemicus".

It seems to us the main task of modern epidemiology to disentangle this Gordian knot, which cannot be unravelled by the sword of an Alexander, but only by long, accurate and troublesome research by us, epidemiologists. The idea of the relative importance of the specific factor in illness seems hard to assimilate. The mission of our generation is not only to localize the distribution of syndromes, that present themselves in an epidemic way, but also to learn to isolate the factors in the spectrum of conditions that are co-responsible for their occurrence. And as these factors are partly of internal, partly of external character, this work can only be done in close co-operation between clinical and field-workers. The task that lies ahead is a combined clinical and a social medical one.

J. N. Morris [6] in an article not long ago hinted at possibilities "of a new era of collaboration between public health workers and clinical medicine," and expresses as his opinion that epidemiology might offer possibilities in this direction, in bringing the two categories to a sound solving of public health problems. In our opinion this is right. We are deeply convinced that a disease has never been brought to extinction by attempts of doctors alone to treat every sick individual. Here public health activities must help.

The task of clinical medicine is to isolate the problem unit to describe the processes that underlie them, and to develop methods to handle and if possible to solve the problem in the individual case.

The task of the epidemiologist is to help both the clinical and the social medical worker; in collaboration with the clinical research workers he has to describe deficient adaptation form in such a way that the clinical description reduced to a countable unit, can serve as base for statistical manipulations and as a base for public health policy. The development of this second part of his task has to be done together with public health men. Sunier will give an example of this combined attack on the complicated neurosis problem.

And so we come to a summary of the modern aspect of the tasks of epidemiology, to my opinion that part of epidemiology that has to deal with isolation of factors and study of interrelations of the factors and conditions, which determine frequency and distributions of a disease in a population.

The *isolation* of these factors and conditions has to be performed together with clinical and social workers. It will bring an extension to clinical work. The *measuring* has to be done together with statisticians, the *handling* together with public health workers.

Epidemiology following this conception can largely contribute to the very much needed integration of social and clinical medical work.

It took Cl. Bernard 20 years to complete his "principes de la médecine expérimentale." He even left wife and children to fulfill this task. Sunier and I were handicapped as our wives made objections against a similar procedure. Nevertheless we made a start and we hope to develop epidemiology in the above mentioned sense in this Institute. But we must ask you for time before we can show you clear results.

We hope this contact will be the first of a series. Please come back from time to time to help us stay in the right track and to see the results of our work.

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Use of long-term bacteriological observations for epidemiological studies of streptococcal, staphylococcal and meningococcal diseases

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Epidemiological methods have until recent times been used primarily for the study of infectious diseases. There are many famous examples of the success of these methods, which have enabled us to combat the most deadly plagues. This was even possible when the cause of the disease was still unknown, as for example in the yellow fever studies of the years around 1900.

In the bacteriological era of the end of the last and the beginning of this century epidemiological research was based more and more on etiological data. Our thereby rapidly growing knowledge of the spread of infectious diseases often provided us with the means of fighting them with appropriate methods.

It is understandable that these successful methods were also tried in diseases with a less or no contagious character, in order to elucidate the influence of environmental conditions on the incidence of the disease and thereby, maybe, give some insight into its etiology. These methods which are now practised on an ever growing scale sometimes did lead to finding the cause of a disease. A recent example of this is the elucidation of the relation between lungcancer and cigarette smoking.

However, I think that it is appropriate to mention here that the application of epidemiological methods to the study of diseases of unknown origin is not new, but the continuation of an old line of research.

In 1897 in the former Dutch East Indies Vorderman emphasized, as a result of an epidemiological study in a number of prisons, that beri-beri – which killed thousands of people – was acquired in closed communities only, when polished rice was the main food. It was an epidemiological observation of Eijkman[1] in 1889 on the relation of polyneuritis in chickens and the sort of rice fed to the birds, which called Vorderman's[2] attention into this direction. Continuation of the work of Eijkman and Vorderman enabled Grijns[3] to formulate for the first time in 1901 this now so well known concept of avitaminosis with the words: "There is much to be said for the explanation that we have to do with a partial starvation" and that beri-beri might be a deficiency disease. So the foundation of the science of vitamins was laid by epidemiological observations. It is impressive to read how much care Vorderman took to obtain unbiased results.

Let us hope that the epidemiological studies of recent times will be as fruitful as these old ones.

But also in the epidemiological studies of infectious diseases new developments have taken place. Through the elaboration of more sensitive techniques for isolation of some pathogens we are now much more aware of their presence in our community. We have had to change our conception of the epidemiology of salmonellosis since our improved isolation techniques have shown a much wider spread of these microorganisms than was formerly suspected.

The recognition of the existence of a great number of well defined types of certain bacteria has provided us with a growing understanding of the relation of these microbes to their host: Man.

To give a recent example: phage typing of staphylococci has enabled us to prove that staphylococcal influenza-pneumonia is not primarily caused by certain aggressive types of these cocci. The distribution of the various types of staphylococci in this severe con-

dition is approximately the same as that found in the nose of normal population groups. This is of epidemiological importance and throws quite a different light on the advisibility of penicillin prophylaxis.

Long term studies on the prevalence of the various types of certain bacteria on the upper respiratory tract of groups of healthy people living in closed communities or apart, have given us a new insight in the epidemiology of the diseases caused by these microbes.

In my laboratory I have had the opportunity to study with a group of assistants and co-workers the spread of streptococci (Zanen, Wagenaar, Van Toorn), staphylococci (Van Toorn, Borst, Ratulangie) and meningococci in healthy people during longer or shorter periods. The streptococci were typed by serological methods (precipitation, agglutination), the staphylococci by phage typing and the meningococci by agglutination.

Zanen in collaboration with Wagenaar and Van Toorn was able to prove that in a group of 40 children of 2 to 9 years living closely together in a home – during a period of observation which for some lasted three years – various types of streptococci of group A spread in epidemic waves, generally invading the throat of practically all the children present. Clinical manifestations of the infections were, however, infrequent.

Generally the children freed themselves of the cocci after a few weeks. When later the same type of streptococcus was introduced again into this community only the children that were newcomers were infected. Those who had already had contact remained free with only two exceptions. However, one of these had been treated with penicillin and may, thereby, not have made enough antibodies.

A few children developed scarlet fever, all caused by type 14 which at that time was in Amsterdam the most frequent cause of this disease. However, a number of children carried this type of streptococci without showing clinical symptoms.

Type 12 which is generally considered to be a nephritogenic strain also spread through this community, causing otitis in two children but no nephritis at all. Microscopical examination of the urine of these children never revealed erythrocytes.

For comparison the spread of streptococcus types was also studied among adults. A group of 20 laboratory workers living separately was chosen and 35 men living in an old people's home. During a period of observation of 7 months in the latter group no waves of infections of streptococci of group A were observed. Two types of streptococci were isolated among the men in this group and no more than 5 men were found to carry streptococci of group A at any time. However, strains of group G spread on a larger scale during the same period, giving a maximum of 10 carriers at the same time, all without clinical symptoms. Among the laboratory workers there were a few constant carriers, some were always negative, others acquired streptococci of group A during the investigation. But never more than one third of the group was positive.

In both groups of adults change of type or a new infection with streptococci of group A more often caused clinical symptoms than in the children.

The observations in both closed communities strongly suggest that each individual has to build up a type-specific immunity which starts in youth and takes a shorter or longer time, depending on the more or less frequent exchange with other peoples flora of the respiratory tract. Generally people free themselves of the cocci, a few remain constant carriers.

We do not know what condition of man enables the microorganism to demonstrate its pathogenicity. May be adults react more easily with clinical symptoms than children do, or perhaps children have as many symptoms but take less notice of their complaints? (H. C. Zanen[4], H. C. Zanen, S. Wagenaar, S. Ganor, M. J. van Toorn[5,6]).

The observations on the spread of staphylococci in the noses and throats of part of the

same group of children are in sharp contrast to those of the streptococci. Whilst the waves of streptococcal infections followed each other in succession, staphylococcus nose and throat carriers remained fairly constant in number (Ratulangie, Van Toorn).

Some children were positive for a long time, others rarely or never. On 269 occasions throat and nose swabs were taken simultaneously. 38,5% of the throat cultures were positive and 59,3% of the nose cultures.

Phage typing of the staphylococci showed that there was some exchange of types but an epidemic spread of one type in most of the children was never observed. This is true for throat carriers as well as for nose carriers. Van Toorn found that only in 14 out of 266 examinations, a different type was isolated from nose and throat (5,2%).

Longterm studies in healthy adults working in a maternity clinic (Borst) gave the same picture. Adult people, when carrying staphylococci, generally retained their own type for a long time.

As to the aggressiveness of certain types, in the children's home only minor ailments were observed, caused by those staphylococci which were present either in the nose or throat of the same child or in that of other children. Staphylococci of group I which in some hospitals in the Netherlands cause the majority of purulent lesions were the most frequent types among the children. Strains lysed strongly by only phages 80, 81 which are considered by several investigators to be more aggressive than other types, were present in the children's home in different periods but they did not cause special trouble.

These observations prompt the conclusion that the epidemiology of streptococcal infections is different from that of the staphylococcal infections. Perhaps the study of the behaviour of newborns towards the invasion of these potential pathogens will give us an answer as to how these differences can be accounted for.

The third coccus circulating on the respiratory tract which is studied in my laboratory is the meningococcus. Statistical studies have shown that in recent years – up till 1957 – in this country meningococcal meningitis was especially frequent in newborn [7]. In our opinion the most probable explanation is that lack of isolation of the newborn favours contact with adult carriers. Because of the greater susceptibility of the young the earlier the children get contact, the more clinical infections will be observed.

In September 1957 we started a fortnightly examination of the rhinopharynx of 54 laboratory people who are working in two groups with very little contact. In one group of 28 people 12 were carriers of whom 6 were regularly positive. In the other group of 26 people 10 were carriers of whom 6 were nearly always positive. From January 1958 on we have included in this study also a group of 17 children of 3 to 9 years living in the children's home. Up till now only one of this group remained free. However, this child left the home after $1\frac{1}{2}$ month's observation.

It is our experience that negative findings are sometimes caused by faulty technique. If the material is not taken from behind the uvula and without touching the buccal mucosa one may miss a positive culture. Because swabbing of the children sometimes gave difficulties, part of the negative findings will have to be accounted for in this way.

Typing of all the strains has not yet been possible owing to difficulties in preparing type specific sera. So far we have been able to type part of our strains thanks to the generous help of Dr. Sarah Branham and Dr. Patricia Bradstreet. Our preliminary results suggest that in the children's home there is an exchange of strains because after some time of residence in the home three children harboured a different type from the one with which they entered the home.

Among 32 carriers of whom strains were typed we did not find typical strains of type A; 5 strains were agglutinated by sera of the C type and 27 strains belonged to the B type.

From 1956 up till now 17 strains from clinical cases of meningitis were typed, 3 of which

belonged to type A, 9 to type B and 4 to type C. One reacted only with the polyvalent serum of Dr. Branham.

Several investigators have already stressed that epidemic waves of meningococcal meningitis are mainly caused by strains of type A. But the epidemiology of this disease is still obscure. Long-term studies and typing of all strains isolated from patients, contacts and other groups will perhaps help us to shed some light on these problems.

In 1957 we experienced in this country a considerable and unexpected decline of the number of cases of meningitis, which is continuing during this year. So I fear that we will have to continue our work till a new wave will manifest itself: Perhaps another ten years?

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The uses of epidemiology

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The epidemiological method has two interlinked functions derived from one basic purpose. I regard epidemiology as providing the scientific basis on which we can found a logical system of preventive medicine. To this end it can help us decide (1) what to prevent and (2) how to prevent.

The first use, deciding what to prevent, is descriptive. As epidemiologists we should know what diseases affect a population, when they fall heaviest and which groups of the population are primarily affected. I would emphasize the importance of this descriptive function. We behave, in much of our preventive medicine, as if we knew what we were about, but I believe that even in the most sophisticated of countries we are still woefully ignorant. This perhaps, is not surprising.

The descriptive techniques we commonly employ are extraordinarily crude. Mortality traditionally has pride of place. The mortality recording in many countries is carefully conducted and by international agreement we have arrived at uniform methods of handling data, of classification and of tabulation. However, we are painfully aware of the poverty of language and the ambiguity that bedevils the death certification of such an important group of causes as the cardio-vascular-renal diseases. We know of the influence of the presence or absence of diagnostic aids on what is certified, and of the differences between teaching given to medical students at different schools which can affect what they certify thereafter as practitioners in even a small, compact country. We have to admit that it is very difficult to maintain continuity in classification and tabulation over a period of years in mortality data for any one country, and we have to accept very considerable differences from place to place in the completeness and accuracy of death registration itself. Dr. Buma has, for example, drawn the attention to the inadequacy of mortality records in outlining the distribution and extent of alcoholism.

Mortality recording is, therefore, so full of hazards that it falls short, even though from many angles it is one of the most reliable descriptive measures. Its major defect, epidemiologically, is of course that it describes the terminal event in relatively serious illness only and tells us nothing of the beginnings of these conditions, or of milder illnesses at any stage. Morbidity recording might make up for these deficiencies but has even greater disadvantages as routinely practised. Notification of disease is applied, and can be applied, on a limited scale only. Incidental measures, such as sickness absence from insurance records, deal with part of the population only and are primarily administrative, not medical data. Hospital morbidity deals with a selected group and severity of illness and is determined as much by the hospital facilities afforded as by the hospital requirements of a population. General practitioner records are potentially an invaluable source of information but are hardly explored as yet.

One of the best methods of obtaining good descriptive data is the planned survey. An initial survey covering all diseases in a population, or representative sample of it, will give an unbiassed overall picture. This stage is represented by the National Health Survey in the United States and the Survey of Sickness in Britain, both on samples of the total population. The Medical Field Units in Ghana and F.O.R.E.A.M.I. in the Belgian Congo have used surveys of complete populations in scattered parts of their territories to provide this base line information.

As the next stage, investigations of special populations are necessary to give refined descriptive data. These are exemplified by Dr. Ruys' family studies of staphylococcal infection, Dr. Schilling's studies of bysinnosis in the cotton industry, and Dr. Reid's studies

of bronchitis in post-office workers. Such surveys are most successful when they try to obtain information about one specific disease or a limited group of diseases. Only then can precise definitions of the clinical symptoms be established and the uniformity and completeness of recording be checked.

If this emphasis on the descriptive function of epidemiology is felt as academic, I would remark that we recognise the new epidemics of coronary heart disease and carcinoma of the lung, but have to admit we do not know how much of the increase we see is real. We know bronchitis as a major disabling and killing illness in Britain, but cannot estimate the true incidence. We suspect that mental illhealth should be one of our main concerns, but are only beginning to measure the frequency of some of the syndromes involved.

This is the state of our ignorance in highly-developed sophisticated countries. In the under-developed territories the situation is naturally far worse, and yet there is persistent pressure to increase the share of preventive medicine and public health when we are in no position to assign priorities. W.H.O. has recently sponsored a survey in one country designed to provide a skeleton picture of what diseases are prominent. This study has revealed a major area of schistosomiasis although its presence anywhere was previously unsuspected; it has shown that though tick typhus, yaws and syphilis were considered major problems on account of frequent admission to the few hospitals, they are relatively rare in the rural areas which form the bulk of the country. It is difficult to think how reasonable preventive measures could have been applied before this knowledge was obtained.

Epidemiological description sufficient to help us decide what to prevent can have many sides, which may conveniently be classified as historical, geographical and personal.

If we determine what diseases occur and are important now, we take a cross section of the stream of medicine. We cannot tell which are developing, which on the way out. Our concern about coronary heart disease is not just with the high death rates among middle-aged men, but their extraordinary increase in recent years. It is valuable, therefore, to obtain the trends of the diseases we describe. Prof. Ruys has shown us convincingly the value of longitudinal studies in bacteriology. It is important, often in a more general field, to know what diseases existed in an area, to realise, for example, that certain areas of Africa were depopulated by trypanosomiasis, meningococcal infections or onchocerciasis and that these infections might return if these areas were inhabited again. It is equally vital to appreciate what will happen as diseases are controlled, to understand the population problems arising from malaria eradication, or the ageing of a population when the infectious diseases of childhood are eliminated.

The geographical description of disease is almost commonplace, so that geographical pathology is being resurrected in its own right. Studies of the incidence of cancer, goitre, dental caries, cardiac and respiratory disease have shown some startling differences both between and within countries. When this information is allied to study of local characteristics we have one of the more fruitful uses of epidemiology in establishing the cause of disease. The method is limited because sometimes the characteristics which are relevant are not arranged geographically but are mixed within each community. Some of the studies which correlated mortality or morbidity with social or economic indices in different places probably failed because the differences within the areas were as great as those between areas, i.e. the populations were not sufficiently homogeneous within an area.

Personal characteristics of many kinds come into the epidemiological description of disease – commonly used ones such as age and sex; economic or social ones based on income, occupation or expenditure; personal habits such as smoking and drinking; physical characteristics such as weight and blood group. The difficulty with adding these

to the description of patterns of sickness is that although these details may be obtainable for sick patients they are rarely available generally, and a population at risk cannot be established for calculating rates. Often such characteristics can be used only in special surveys.

The description of disease in terms of Wade Hampton Frost's "Time, Place and Persons" prompts questions on what causes the different patterns. In this way the relation between fluorine content of domestic water supplies and dental caries was established. Geographical differences were the basis of the iodine deficiency hypothesis of goitre. Geographical comparisons prompted the dietetic hypothesis of coronary heart disease and have to be considered in any hypothesis regarding the factors influencing bronchitis morbidity. Time trends were part of the unravelling of the aetiology of retrolental fibroplasia which followed excessive oxygen administration to premature babies. Seasonal trends, economic and geographical patterns were combined in Goldbergers's classic analysis of pellagra in the southern United States. The geographical patterns of abnormal haemoglobins led to the fascinating linking of sickling in man withrelative immunity to malaria. Geographical distributions and the personal habit of taking bush teas were the critical characteristics which solved the causation of veno-occlusive disease in Jamaica.

I have given only a few examples of epidemiology used to suggest the causes of disease and factors influencing its distribution. The hypotheses thus prompted had usually to be confirmed by special investigations. I have not attempted to discuss the techniques that can be employed at any of the stages. Rather, I have attempted to show that the essence of epidemiology is, in my opinion, Accurate Description leading to Sound Hypothesis. The failures of epidemiology lie in inadequate clinical and personal observation, the successes in meticulous attention to detail.

Finally, may I put a purely personal view. Speaking of clinical medicine the late Sir James Spence said that the doctor's first job was to advise not to treat – to show the patient how to live with his illness. I wonder whether the wise epidemiologist might not follow the same course. He would be humble in his approach to theories of causation, particularly his own, and would check and re-check before claiming too specifically that he had identified the factor that really mattered. When he had made his epidemiological diagnosis he would not be over-anxious to treat; he would accept that Man must learn to live with some diseases and that his efforts at prevention, if ill chosen, might only aggravate the situation eventually. The problem of hospital cross infection with drug-resistant strains and the indiscriminate use of chemoprophylaxis and chemotherapy should be a warning to all epidemiologists.

Use of epidemiology in determining causation of disease, with special reference to lung cancer

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Among the uses of epidemiology, that pertaining to the etiology of disease is probably most important. This is the case because knowledge of causative factors leads to prevention – the ultimate aim in disease control. In spite of this circumstance, (and one could cite many historical examples of disease prevention through epidemiology – including leprosy, chimney sweeps cancer, scurvey, retrolental fibroplasia, and many others) it is precisely in the consideration of etiology that epidemiology encounters much misunderstanding.

On the one hand epidemiology is denounced as "mere statistics" and the claim made that everything must be proved in the laboratory. As a matter of fact, some discredit has come upon epidemiology because of excessive inferences based upon rather meager statistical associations, e.g., between the mortality rate from coronary heart disease in certain countries and the proportion of calories in the diet of those countries represented by fat.

On the other hand some assert that experimentation on animals in respect to non-communicable disease proves nothing regarding human disease. In support of this latter position one can cite the example of berryllium, a substance given a "clean bill of health" for use in industry after some animal investigation disclosed no harmful effect in the species studied. It was only after several instances of respiratory illness, some fatal, that beryllium was recognized as being highly dangerous to man, even though it seemed innocuous to certain rodents.

Because of the increasing importance of the question as to how epidemiologic investigation relates to knowledge of disease causation, it seems desirable to examine the problem.

One formulation which may be helpful is that such investigation proceeds in four successive steps. These are, of course, not arbitrary. One or another may occur out of order or be skipped entirely. However, the framework of these four steps appears to be generally applicable.

1. – The first step may be termed "sorting out the hypotheses". Ordinarily the epidemiologist approaching a new disease problem finds a number of hypotheses which have been advanced to account for the origin of the disease, sometimes a plethora of hypotheses as is now the case in coronary heart disease. These hypotheses often arise on the basis of the impressions of clinicians and they may be supported by various bits of data.

The first job, then, is to sort out these hypotheses in order to ascertain which seem most likely to yield important results if pursued. In this stage of the development of knowledge concerning disease causation, opinions come strongly to the fore and the literature may become glutted with rather wild claims and counter-claims. How can one proceed systematically, as an epidemiologist?

A useful, and reasonably economical way is to carry out a socalled retrospective investigation. Here the hypotheses which seem most promising to the particular epidemiologist are tested by determining the frequency of certain characteristics, consistent with the various hypotheses, among a group of persons with the disease – and contrasting with the frequency of these same characteristics in a control group which does not have the disease. The magnitude of the differences between the frequency of the characteristics in the case series and in the control series roughly indicates the ranking of hypotheses according to whether they deserve further investigation. Thus, a large difference between the case series and the control series in respect to a certain factor suggests a line of research worth more study; a small difference or none at all would tend to minimize the relevance of the item.

Two advantages of the so-called retrospective method of investigation should be mentioned. One is that it permits the examination of several hypotheses at one time since a variety of questions may be asked in a single interview or questionnaire. The other is that it is a relatively inexpensive type of epidemiological research.

Useful as it is for sorting out and crudely testing multiple hypotheses, the retrospective method does not convince many persons of the correctness of any one idea as to the causation of a disease. Objections can be raised against the design of almost any case-control study.

2.–Therefore the epidemiologist usually proceeds to the second step, i.e., to confirm a particular hypothesis as to excessive risk among persons with a certain characteristic by carrying out a prospective, or longitudinal investigation. For this purpose he assembles information about a group of persons without apparent disease who are categorized as to their degree of overweight, cigarette smoking, exercise – or whatever the hypothesis might be; then the epidemiologist observes and measures the occurrence of the disease being studied among persons with various degrees of the trait in question. He may note that the frequency of disease among those with the highest degree of the characteristic being tested is substantially greater than among persons who do not possess the characteristic, or possess it in lesser degree. This fact leads to the inference that possessing the characteristic carries an excessive risk from the disease. If the range of frequency follows a steep gradient, according to degree of the characteristic, and several studies confirm this fact, many would conclude that a causative factor has been identified.

Experience during the past decade or so with the investigation of cigarette smoking as a factor in lung cancer illustrates quite well the succession and import of these first two steps.

3. – The third step is to isolate the particular physical, chemical or other agent affecting the high risk group which is responsible for initiation of the disease process. Pin-pointing the precise agent greatly advances understanding of the etiologic mechanism and favors the development of control measures with a minimum of change in ways of life. It is in this stage that the experimentalist comes forward to join hands with the epidemiologist. Laboratory investigation with animals may confirm what has been discovered by observation of human populations, and carry knowledge one step further through determining the precise agent in the exposure which is the key to the process. It should be noted, however, that negative results on animal species by no means discredit the findings of human epidemiologic studies. One must always consider the possibility that the particular species used were not responsive to the agent in the same way as humans, or that the method of administration was not effective.

4. –Assuming that the precise etiologic agent has been identified, the fourth step is to institute control measures and assess their effectiveness. In this phase of its application epidemiology becomes a "practical" science, usually carried out by the health authorities. It is the end-result of all that has preceded. Health authorities vary in their readiness to promote control measures indicated by epidemiologic investigation. In general, they are inclined to wait until the third step has been completed since this lends substantial force to any program of action. Sometimes – and very appropriately – health authorities are willing to proceed on the basis of clear-cut evidence from the second step, i.e., confirmation of a very high risk among persons suffering a particular exposure, even though the precise responsible agent in the exposure has not yet been identified.

This four-step pattern may be observed in connection with the research on cigarette smoking as a factor in lung cancer.

Investigation by the California State Department of Public Health of possible occupational factors in this disease is following a similar pattern. Certain occupations have long been known to bear an etiologic relationship to some cases of lung cancer, e.g., mining at

Joachimsthal and Schneeburg, and chromate ore operations in the U.S.. Additional occupational exposures have been suspected and the suspicion supported by some evidence, e.g., exposures to asbestos, arsenic and certain hydrocarbons. It seemed desirable to pursue this matter.

As the first step in studying occupational factors in lung cancer as it occurs in California, more than 500 hospitalized patients with lung cancer proved histologically were interviewed as to their life-long job history.[1] Interviewers who were skilled in job analysis obtained detailed information as to each occupation in which the patient had been employed. Data on cigarette smoking and other hypotheses were also secured. The interviewers recorded identical types of information for a control group, matched as to age, sex, race and admission to the same hospital.

The findings as to cigarette smoking confirmed those of many similar studies. In addition, several occupations stood out with much greater frequency among the case series than in the control group. These included welding; painting; lead, zinc and copper mining; commercial cooking; marine engine-room work; steam-fitting; and electric bridge-crane operations. Review of the literature revealed that many of these occupations had been identified as suspected factors in lung cancer by three other investigations using different techniques.[2]

Therefore, we proceeded to the second step in the epidemiological study. This was to assemble sizeable populations of men engaged in the suspect occupations with a view to observing prospectively the occurrence of lung cancer among them, as compared with that of men in non-suspect occupations and in the population at large. It was necessary to obtain the information (brief occupational history, cigarette smoking, and details about current occupation) from thousands of men in each suspect occupation in order to get a sufficient volume of lung cancer experience for analysis within a reasonable period of time.

In gaining access to men in the selected occupations and in achieving a satisfactory response to a mailed questionnaire, the trade unions proved immensely helpful. With their support, and three mailings of the questionnaire, about 85 percent were returned from each of dozens of local unions that participated in gathering the base-line data.

The observation of lung cancer experience is now only in its second full year – too early for definitive results. However, the initial observations have not discouraged us from continuing. In another year or two, the findings should be adequate to confirm or refute the hypothesis that certain of the occupations play an etiological role in lung cancer.

If confirmed, the time will be at hand to undertake the third step in the research – the isolation by laboratory investigation of the specific agent involved in the disease-causing process. (Already some experimental oncologists in California have shown considerable interest in the findings and have started preliminary work.) Then one can proceed to the fourth step in the epidemiologic approach to disease causation and prevention, the development and application of control measures.

This brief outline of a four-step pattern in the advance of knowledge concerning the etiology of disease may indicate the underlying logic of the process, and help to minimize unnecessary controversy as to which steps "prove" causation.

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Field surveys: objectives, definitions, sampling and observer error

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The main objectives of the field survey are:

a. To find out the extent of a disease in the community, i.e. prevalence studies.
b. To find out how the incidence of a disease is changing in a community, i.e. repeated surveys of a population over a period of time.
c. To compare one group with another in the search for causes.

These are three of the more important uses of the field survey. There are others, such as surveys to assess the utilization and need of a service and surveys to assess the quality of a service.

Surveys designed to try and discover the prevalence of a disease in the whole population are sometimes unrewarding. It is usually clear from clinical experience that certain age or sex groups are immune or nearly so and it may therefore be a waste of time to examine a large number in these groups. The prevalence survey therefore often narrows down to a decision to investigate the prevalence of a condition in a specified population group, e.g. home accidents in children under five or of heart disease in middle-aged and elderly men.

In carrying out field surveys it is advisable to have a clearly formulated and limited *hypothesis* it is desired to test. Too many surveys are undertaken on too broad a basis and too many questions are included in the questionnaire. Often in such surveys a mass of data is accumulated which turns out to be irrelevant and which has to be discarded and few of the differences which are found, are statistically significant because of small numbers. It is probably more profitable as a rule to ask only a few questions and to study a lot of people than to ask many questions and thereby greatly to reduce the number of people it is possible to study.

Before any field survey designed to measure the prevalence of a disease can be undertaken, the condition to be investigated must be defined as precisely as possible.

As soon as we embark on prevalence surveys we are likely to run into the difficulty of the borderline case. The normal merges into the symptomless or pre-clinical stage and the symptomless into the stage of early indefinite symptoms and so on until the advanced or terminal stage is reached.

Some illnesses have a relatively clear-cut clinical phase, for example, acute specific conditions, such as measles. In others, a laboratory measurement makes possible an arbitrary division between normal and abnormal and facilitates the definition of a disease for epidemiological work. It is dangerous to place too much reliance on a laboratory test, however, unless the variability inherent in the test itself is known. For example, it might appear quite reliable to base a field survey of hypochromic anaemia on haemoglobin estimations. Macfarlane, King, Wootton and Gilchrist[1] (1948), however, showed that the co-efficient of variation in a haemoglobin estimation (Haldane method) carried out by 16 observers was 9. This means that one half of the observations will vary from the mean value by 6 per cent. or more, one fifth by 12 per cent. or more, one tenth by 15 per cent. or more and one twentieth by 18 per cent. or more.

Where clinical definitions are relied upon, these should be written down in precise terms, e.g. someone has chronic bronchitis "if they have had a cough and sputum lasting for at least one month every winter for the last three years and there is no other respiratory disease to account for it".

The most difficult types of illness to define are probably the various kinds of mental illness and we very much need better definition in this field if epidemiology is to contribute usefully to it.

Epidemiology has always depended heavily on the laboratory for its advance and in particular on bacteriological and immunological techniques. Today in the field of non-communicable disease we are using various laboratory tests to help us to define the existence and severity of the conditions we are interested in. Dr Charles Fletcher, in his paper to the Study Group at Noordwijk in 1957 laid down four criteria for such a test:
1. It must be valid; that is, it must detect or measure what is relevant to the study.
2. It should be simple if it is to be used on large numbers in the field.
3. It must be repeatable. The same and different observers should get approximately the same result on the same person.
4. It should be discriminating. This can be measured by comparing the difference between the mean values found in the two population groups under study with the S.D.'s of the values in each group.

In every sort of field survey some sort of objective test should be included if possible as it greatly adds to the value of the results by making comparison between different surveys more reliable.

There are occasions when it is strongly suspected that there is a high incidence of some condition in a restricted population and it is necessary to demonstrate this in order to get something done about it. If possible, the whole group should be examined. This might be done if the community consisted of a residential school and it was suspected that there was a high incidence of pediculosis capitis for example. Usually, however, the whole population concerned cannot be examined and then some procedure of *random sampling* has to be adopted. For example, Ogilvie and Newell[2] (1957) in their study of bronchitis in Newcastle on Tyne, arranged for health visitors to visit every fortieth house in the city to discover cases of chronic bronchitis and thence after checking these cases at hospital to work out prevalence rates. The street directory or electoral register is valuable for this purpose and it is necessary to decide beforehand which houses are to be visited. Doctors lists are valuable when they contain the names of 98% of the population as in Great Britain.

If it is hoped to make comparisons between sub-groups within the sample, e.g. age or social class groups, it may be advisable to take a *stratified sample*. For example, if a social class comparison is required, it may be necessary to examine a higher proportion of social class I (Professional and Managerial Classes) than would be found in a random sample.

The problem of "*refusals*" or "unobtainables" is difficult. Should the gaps be made up from an alternative list or not? In any case it is advisable to get as much information about the refusals as possible, e.g. age, sex, occupation and address and the reason for refusal. In this way it may become clear that the refusals are similar to the examined group as regards the characteristics which have been checked and it may be deduced (with varying degrees of confidence) that they are therefore unlikely to differ from those examined in respect of the condition under study. A.L. Cochrane et al have shown that with persistence it is possible to obtain acceptance rates of 90-98 per cent in field surveys.

In the sort of study when two groups are being compared in the search for clues as to causation, it is of value to have a rough idea of the prevalence of the condition in the "normal" population and in the group under study. If these proportions can be estimated,

for example from a pilot study, then the size of the samples that will have to be examined in order to establish a significant difference (say at the 5 per cent. level) can be calculated. In practice, the size of the sample it is decided to examine, is often based more on considerations of cost, time and available manpower. My colleague, D. Kerridge, has worked out a table (*Table 1*) which indicates the *sizes of samples required* to establish statistical significance at the five per cent. level for different results. He has done this in the form of a therapeutic trial but it would be equally appropriate to a prevalence survey in two contrasting population groups.

Table 1

The table shows the *approximate size of sample*, containing roughly equal numbers of ‚treatment' ("A") and 'control' ("B") subjects, which must be taken to obtain a significant result (at the 5% level) nine times out of ten, in a double sided test, when the affected percentages in the two groups are as shown in the margins.

		Percentage of the "B" population affected				
		5	10	15	20	25
Percentage of "A" population affected	5	–	553	162	83	49
	10	553	–	934	254	123
	15	162	934	–	1210	330
	20	83	254	1210	–	1480
	25	49	123	330	1480	–
	30	34	73	156	393	1713

When the proportions of "A" & "B" subjects in the sample are not equal, the total required will be larger.

Calculated from tables due to Patnaik (1948) Biometrika vol. 35.

Another point is the *observer error*. I am not sure that "*error*" is the right word to use. While some of the differences between two observers are due to a mistake on the part of one of them, more often it is simply the question of two different interpretations of the same observations. The error may be intra- or inter-observer. Fletcher and Oldham[3] (1949) showed that experienced radiologists differed considerably among themselves in judging chest radiographs in respect of certification for pneumoconiosis benefit.

Cochrane, Chapman and Oldham[4] (1951) studied observer error in relation to rerpiratory symptoms and a history of respiratory disease. Four observers each questioned sandom samples of about 250 coalminers with regard to the presence or absence of cough sputum and breathlessness and whether they had had bronchitis or pneumonia in the past.

There were considerable differences in the incidence of respiratory symptoms in the three groups as judged by the different observers, but the incidence of previous bronchitis and pneumonia was much the same. This indicates that the elicitation of respiratory symptoms is very liable to observer error but that the incidence of previous attacks of bronchitis or pneumonia can be reliably judged on the basis of answers to a simple question such as "Have you ever had pneumonia?".

Schilling, Hughes and Dingwall Fordyce[5] made a valuable and detailed study of observer error in the diagnosis of byssinosis. In their study two observers each examined all the 187 subjects. Their estimate of the size of observer error was the percentage of the 187 in whom the two examiners disagreed. For various chest signs this figure varied from

4 to 30 per cent. Agreement on the question of presence or absence of byssinosis however reached the high level of 93 per cent.

It is difficult to know in advance what symptoms or signs are more or less *reproducible*. Examples may be taken from a recent survey of five-year-old school children carried out by Dr. Marjorie Clifton and myself. The object was to measure the incidence of respiratory disease in groups of children living in different parts of the city of Sheffield and subject to different levels of air pollution.

Table 2 Agreement between two observers

Physical signs in the chest

Observers	Total Examined	No added sounds in the chest	Added sounds in the chest			
			Crepitations	Sibillant Rhonchi	Other Rhonchi	Combination of added sounds
MC	499 *100%*	411 *82%*	4 *1%*	13 *3%*	53 *11%*	18 *3%*
JP	165 *100%*	134 *81%*	2 *1%*	4 *2%*	21 *13%*	4 *3%*

A survey of 664 five year old school children

Table 2 shows the *degree of agreement* on the incidence of physical signs in the chest obtained in examining two random samples from the same schools. (The examinations were carried out in the early winter when British 5-year-olds have quite a lot of bronchitis.) We had discussed the physical signs before the examination and carried out a few examinations in duplicate and compared our findings. Even so, we were surprised to find so high a degree of agreement on the prevalence of these physical signs in the two samples.

Table 3 Agreement between two observers

Size of Tonsils

Observers	Total Examined	Estimated width of tonsil protruding from anterior fauces					
		Not visible or normal	$\frac{1}{4}''$	$\frac{3}{8}''$	$\frac{1}{2}''$	$\frac{3}{4}''$	Not seen
MC	499 *100%*	138 *28%*	207 *41%*	88 *18%*	60 *12%*	0 *0*	6 *1%*
JP	165 *100%*	93 *56%*	44 *27%*	16 *10%*	11 *7%*	1 *0,6%*	0 *0*

A survey of 664 five year old school children.

Table 3 shows our agreement or rather our *disagreement* on the estimated size of tonsils. Obviously our standards here were at variance.

Agreement on the final diagnosis, using the crude divisions of "No respiratory infection", "Upper respiratory infection" and "Lower respiratory infection", was quite close (*table* 4).

Tabel 4 Agreement between two observers

Prevalence of respiratory infection

Observers	Total	No Respiratory Infection	Upper Respiratory Infection	Lower Respiratory Infection
MC	499 *100%*	188 *38%*	196 *39%*	115 *23%*
JP	164 *100%*	52 *32%*	66 *40%*	46 *28%*

A survey of 663 five year old school children

Perhaps the lesson to be drawn from this is that the best chance of getting agreement between observers on the prevalence of some clinical condition is to break it down into its component symptoms and signs, to grade conditions by severity where possible, and to try and get agreement on these components of diagnosis first. Once this is achieved, the decision as to whether the findings add up to the clinical condition in question can apparently be done in a repeatable way if a clear definition of the clinical condition in terms of the symptoms and signs has been previously agreed upon.

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Field surveys of byssinosis in the Lancashire cotton industry

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The aim of these surveys was to elucidate the aetiology of byssinosis and to assess its prevalence and severity in the English cotton industry.

More than 100 years ago, English cotton workers were known to suffer unduly from byssinosis, a chronic respiratory disease caused or at least aggravated by exposure to dust at their work. Following several enquiries, notably those of Collis [1] (1909), Prausnitz [5] (1936) and two government committees (Home Office [3, 4] 1932 and 1939), a compensation scheme was initiated in 1941 for English cotton workers. Nevertheless, the aetiology of byssinosis still remained obscure. The causal agent in the dust had not been discovered and the mode of action of the dust was not understood.

The symptoms of byssinosis are so unusual that some doctors have doubted their veracity. After some years, the patient notices that his chest feels tight on Monday afternoon or on the first day at work after an absence. His symptoms disappear after he has been at home for an hour or so. On Tuesday and other working days he feels well and has no symptoms. He may continue in this way for years without getting any worse, or he may get progressively worse and have chest tightness and breathlessness on Tuesdays, then on Wednesdays and so on until he is affected on every working day. Eventually, he has permanent effort intolerance. At this stage, he may have an aggravating cough with or without sputum.

It so happens that the English cotton industry is concentrated in the county of Lancashire where the prevalence of chronic bronchitis is exceptionally high (Goodman, Lane and Rampling [2], 1953). Both radiography and pathology supported the notion that byssinosis might well be chronic bronchitis, aggravated by exposure to dust in the mills rather than an industrial pulmonary disease with a distinct pathogenesis of its own. For there are no specific x-ray changes in the lung fields and the few studies of the pathology of byssinosis report findings such as chronic bronchitis and emphysema.

Although it was believed that as a result of dust control in the mills, chronic respiratory disease among cotton workers was a diminishing problem, a preliminary field survey made about 10 years ago revealed a high prevalence of chronic respiratory disease in middle-aged cotton workers most heavily exposed to the dust (Schilling, Goodman and O'Sullivan [7], 1952).

In the light of these facts, it was decided to undertake a detailed field survey of the Lancashire cotton industry. This was the only way to determine the prevalence and severity of byssinosis and at the same time, it would be possible to assess the veracity of the symptoms of byssinosis and find out more about the mode of action of the dust.

As a first step, those workers most likely to suffer from byssinosis were studied, namely, men aged 40-59 years working in the card and blow-rooms which are reputed to be the most dusty departments in a cotton mill. The survey was confined to mills spinning the coarser and dirtier types of cotton. Men of the same age, employed in 2 engineering factories situated in the same town as the mills served as controls.

In the defined populations there were 202 cotton workers and 100 controls, of which more than 95% were included in the study.

To test the reliability of the histories, two observers examined each man independently and graded him for byssinosis as follows:-

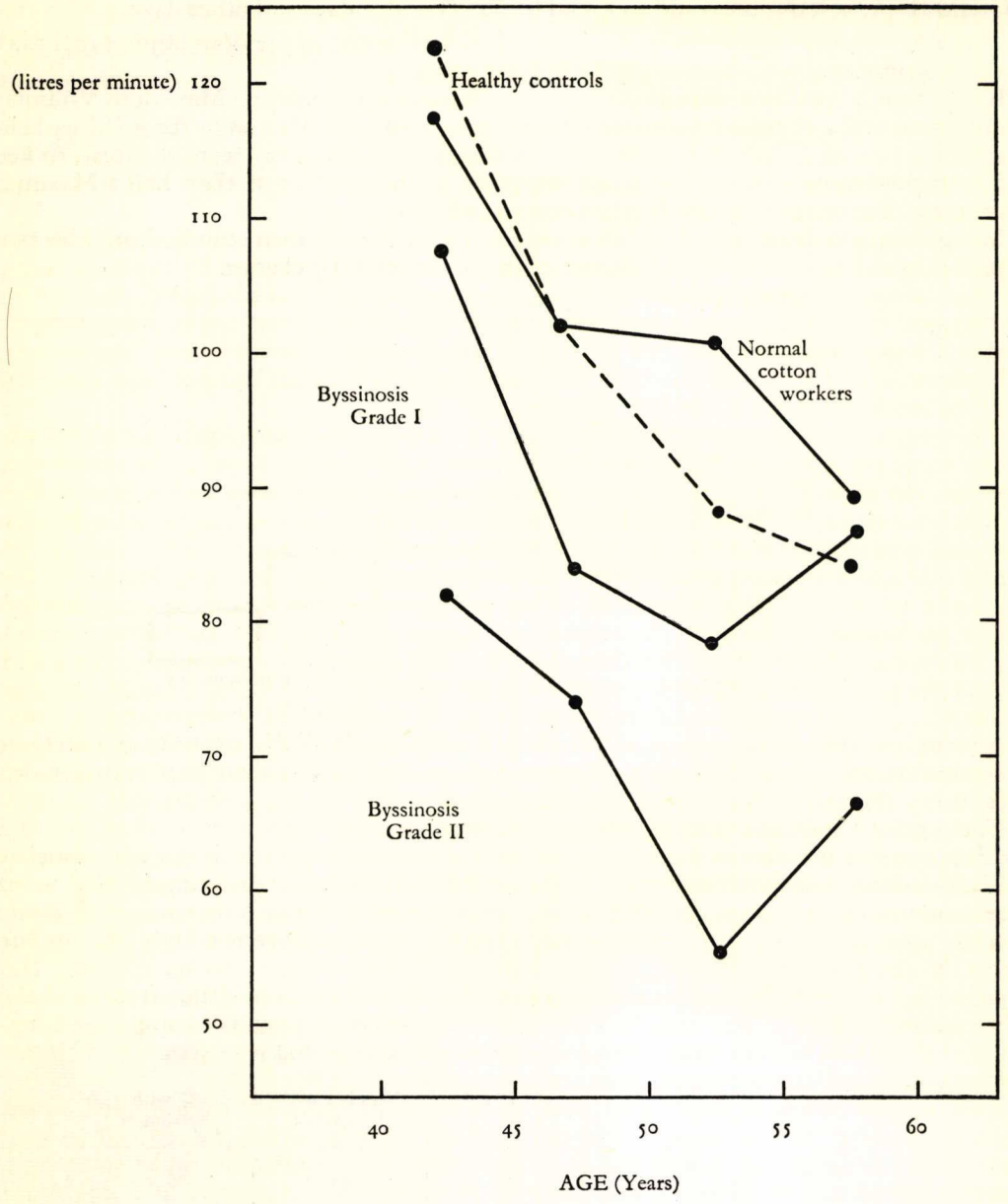

Fig. 1. Mean maximal voluntary ventilation (indirect) of cotton workers and healthy controls

Normal: no chest symptoms;
Grade I: chest tightness and/or breathlessness on Mondays only;
Grade II: chest tightness and/or breathlessness on Mondays and other days.

These two grades were included because it had been noted in previous studies that as the disease progresses, symptoms extended beyond Mondays.

In addition, a modified Gaensler apparatus was used to measure Maximum Voluntary Ventilation and a standard questionnaire to grade dyspnoea. Men were recorded as being seriously disabled if they were unable at the weekends, when away from the dust, to keep up with normal men of their own age walking on the level or if they had a Maximum Voluntary Ventilation of less than 50 litres per minute.

The gradings of byssinosis were identical in 76% of the 183 men seen by both observers *(table 1)* which is very much more than might be expected by chance.

Table 1 - Comparison of byssinosis gradings in 183 cotton workers

		Observer A		
	Byssinosis Grade	N	I	II
Observer B	N	72	6	—
	I	6	47	17
	II	1	14	20

Complete agreement in 139 men (76%). Agreement on the presence or absence of byssinosis: 139 + 14 + 17 = 170 men (93%).

Age for age, the average Maximal Voluntary Ventilation (M.V.V.) of the men with Grade I byssinosis was lower than normal cotton workers and higher than men with Grade II byssinosis *(fig. 1)*.

These results indicate that the unique symptoms of byssinosis were unlikely to be an artifact because the histories given by the cotton workers were consistent and associated with a decline in respiratory function. Of the 88 men in the engineering works, 12 had symptoms of chronic bronchitis but none gave the typical history of byssinosis. Although cotton workers with advanced byssinosis usually have persistent cough and sputum, most of those in the early stages of the disease had no cough and no sputum. Thus, byssinosis, particularly in its early stages, was found to bear little resemblance to chronic bronchitis. It was only in its later stages when it may be complicated by a

Table 2 - Prevalence of byssinosis in card-room workers aged 40-59 years

	Number at risk	Number with byssinosis	% with byssinosis
On Carding Engines	35	24	69%
Near Carding Engines	109	51	47%
Distant from Carding Engines	109	25	23%

$\chi^2 = 27.33$; $n = 2$; $P < 0.001$

superimposed infection that it was difficult to distinguish it from chronic bronchitis. Of the 190 men seen, 60% had byssinosis and 23 (14%) were seriously disabled by it. The proportion of the controls seriously disabled with respiratory disease was 4.5% (Schilling, Hughes, Fordyce and Gilson[8], 1955).

As the prevalence of byssinosis was so high among the men working in the card-rooms, the survey was extended to other cotton workers, in the same mills and in other mills spinning different types of cotton. These studies revealed an interesting distribution of disease, within the mills and for the different types of mills. The nearer working groups were to the carding engines, the higher was the prevalence of disease *(table 2)*. An obvious deduction was that the carding engines were the main source of the dust causing the disease, inferring that existing methods of dust control were unsatisfactory. In mills spinning fine cotton, the prevalence of disease was significantly less than in mills spinning medium and coarse cotton *(table 3)* (Schilling, 1956).

As these epidemiological findings indicated that there were likely to be consistent differences in the concentrations of airborne dust in different types of mills and in different

Table 3 - Prevalence of byssinosis in men aged 40-59 years in different types of mills

Manufacture	Number at risk in card-room	Number with byssinosis	% with byssinosis
Fine cotton [1]	51	18	35%
Medium cotton [2]	75	46	61%
Coarse cotton [3]	75	52	69%

[1] Counts of 57 or more (the count is the number of hanks of 840 yards in 1 lb. of cotton)
[2] Counts of 27-56 [3] Counts of less than 27

$$\chi^2 = 15.06;\ n = 2;\ P < 0.001$$

parts of the same mill, a further survey was made to measure the relationship between prevalence of disease and dust concentrations. Its object was to try and identify the causal agent and the size range of the particles causing the disease and at least to determine safe levels of dustiness in the cotton industry.

The most accurate method of relating prevalence of disease to dust exposure is to study prospectively a group of workers from the time that they first enter a dusty trade. Variations in the dust concentrations to which they are exposed can then be measured and their total dust exposures accurately assessed.

As byssinosis takes a long time to develop, such a study would take many years to complete. Therefore, a quicker though less reliable method was adopted. A group of mills was chosen in which the layout and spinning methods had not changed substantially for 25 years. Detailed occupational histories of the operatives in these mills were taken and, on the assumption that the present concentrations of dust were a reasonable index of past concentrations, their total dust exposures could be calculated. The measurement of the dust presented technical problems. It was necessary to use an instrument which was easy to operate and required little attention. Although it has been assumed previously that byssinosis is caused by the fine dust, that is to say particles less than 7μ in diameter which are

deposited in the alveoli (Prausnitz [5], 1936; Schilling [9], 1956), the clinical and physiological effects of cotton dust indicate that the bronchi and bronchioles are affected. Thus, it was necessary to measure the concentrations of the coarse and the fine dust. The Hexhlet described by Wright [10] (1954) was adapted for this purpose.

Since the cause of byssinosis was not known, the dust was analysed to derive indices of the concentration of its main constituents: (1) broken cotton fibres; (2) plant debris; 3) minerals from the soil.

The relationship between exposure to these various constituents in the fine and coarser dust fractions and the prevalence of byssinosis will be considered.

The importance of the fine dust will be measured experimentally by exposing volunteers to all the dust and to dust from which particles larger than 7μ in diameter have been removed. The effects of these exposures will be assessed by measuring changes in ventilatory capacity and clinical symptoms.

The methods used in this survey and the results will be fully described elsewhere (Roach and Schilling [6]).

Conclusion

The field survey is a method of reconnaissance and may do no more than measure the prevalence of a disease; but if combined with studies of the environment, it may also elucidate the aetiology of disease and determine safe levels of exposure to dust or other noccuous agents.

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The use of absenteeism records in epidemiology

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The word "epidemiology" literally means "science (of things) over a people".

To conform with the word "people", the term "population" has to be supplied with a time-dimension and its human quality has to be stated explicitely. Then the definition becomes:

Epidemiology is the science of distributions over a field, that is the product of time and some human population.

The field in question is a collection of man-histories. Its natural unit is the man-day. The matter that should be distributed over this field is not specified by the definition, but in the case of absenteeism records it is spells, either of sickness or accidents. Thus absenteeism records may be considered as indispensable tools for that branch of epidemiology, which deals with absences, mostly with the practical purpose of improving the government of human absence-behaviour in some special case and respect.

No tools are made without any idea about their use and no absenteeism data are recorded or statistically arranged without some notion about the epidemiological purpose they could serve. Let the collection of possible purposes be restricted to those, connected with the proper care, that ought to be taken of the human equipment of larger factories and other plants. This is the type, which the statistical department of this institute is often confronted with.

Then the human component of the field must be the population of the workers of a certain concern or collection of concerns. It may be subdivided in several ways, depending on the recorded characteristics of every worker. In our routine statistics these are scanty, namely concern, sex, hand- or head-worker and, only in our diagnosis statistics, age. But the internal statistics of the concerns sometimes contain much more valuable information, such as department, profession, distance from home, dates of entry and exit. The latter characteristic is of special importance, since it enables the restriction of the population to individuals observed throughout the period of observation, which is indispensable for the study of clusters of spells in certain individuals. This approach was introduced by Major Greenwood in 1920 and is connected with the concepts of accident- and absence-proneness.

The time-component of the field is always restricted in practice to a certain interval, the period of observation. Owing to labour turn over, the number of workers is not constant over this period, unless the population has been restricted as mentioned. The size of the field, or one of its sub-fields is taken as the product of the period of observation and the average number of workers of the population or one of its sub-populations. Many statistics of spells make sense only, if taken in relation to the size of the corresponding field. It is worthless, for instance, to record for each spell the age of its sufferer, if the average age-distribution of the population of workers is unknown.

The spells are the elements of the distribution over the field. They have three groups of recordable characteristics.

First, those relating to the sick persons involved, which should always be accompanied by the corresponding records of the population. Every sub-division of the population of workers induces a similar subdivision of the distribution.

Secondly, two characteristics relating to the time-component, namely the time of inception and the time of termination, or the duration. The decision whether a spell belongs to the field, depends on these time-characteristics. There are three possible decisions. Or

the time of inception should be included in the interval of observation, or the same should apply to the time of termination, or the spell should coincide at least partially with the period of observation.

Thirdly, the characteristics relating to the spell as a whole, such as diagnosis or medical care. Characteristics of the second and third kind *may* be considered independently of field sizes. The annual reports of our diagnosis statistics include frequency distributions of spells according to diagnosis and according to duration, both specified for age. It is sometimes objected that, for instance, the number of spells labelled as diseases of heart and vessels, or the number of one-day-spells is more interesting if taken per man-year than if taken per hundred spells. But then it is often overlooked that the main facts should be considered before entering into details. Before comparing the diagnoses or durations of two factories or departments, the numbers of spells per man-year should first have been compared. If it is already known that the number of spells per man-year in one factory is twice that in another factory, this same fact interferes with all other comparisons of frequencies per man-year. If the number of one-day-spells per man-year is also twice that of the other, it should be remembered that this is only what was to be expected, but if the numbers were equal it should be observed that this is fresh, unexpected information. On the other hand, if comparisons of numbers per hundred spells are compared, every striking difference is a new piece of information. An illustrative example is described by Dr. M. J. W. de Groot of our statistical department in a recent issue of *Mens en Onderneming* (1958).

In a certain factory the numbers of heart-diseases per man-year in the departments were compared and in one department it appeared to be considerably higher than in the other departments. After several fruitless efforts to find a reasonable explanation, it was discovered that the number of spells per man-year was also considerably higher for all other diagnosis groups. As soon as it had been realized that the fact had nothing to do with hearts in particular, the bad human relations in the department concerned were recognized as a very likely cause.

The number of spells per man-year is called the incidence rate. It has been mentioned as a principal statistic, that should be considered before entering into detail. It is one of the two statistics, that we are receiving from and redistributing to hundreds of concerns weekly. It is expressed per hundred man-weeks instead of one man-year, which is more convenient for the weekly routine.

The other principal statistic is the number of man-days of the spells per hundred man-days of the field, which is called the sickness rate. Of course the latter statistic does not change if the man-days are replaced by man-weeks or man-years. The information given by these statistics, the incidence rate and the sickness rate, are rather independent. If a scatter diagram is made of these rates for the hundreds of plants, it appears that there is very little association. If we are informed that in one factory the incidence rate is higher than in the other we cannot predict with any certainty that the sickness rate will also be higher. The sickness rate is the more stable in time. Accordingly the incidence-rate is the more responsive to changes in the environment.

As an illustration of this rule another example by Dr. M. de Groot may be cited. In a certain concern the cancellation of one waiting day for the restitution of lacked wages was followed by a sharp increase of the incidence rate whereas the sickness rate remained almost the same. If the waiting day had prevented a number of spells of short duration, its abolishment should in fact sharply be reflected in the incidence rate and only faintly in the sickness rate. However there is also reason to believe that the waiting day had not so much prevented spells as linked them together. The average duration, being the quotient of the sickness rate over the incidence rate, is correlated positively with the sickness rate and

negatively with the incidence rate. It is about as responsive to changes as the incidence rate. In the previous example the abolishment of a waiting day was followed by a sharp reduction of the average duration. With smaller concerns both the average duration and the sickness rate are subjected to rather large random fluctuations, since they heavily depend on a few spells of very long duration.

Absenteeism records can render two kinds of services to epidemiology: they pose questions and they sometimes help to find answers. In the present, rather embryonal, stage of this branch of epidemiology they pose too many questions and give too few answers, resembling too much the general impressions which, according to Francis Galton, are never to be trusted. Every significant difference or change of sickness- or incidence rates poses the question as to its origin. Dr. Ekker of our statistical department, is hunting for answers in the most inexpensive way, namely by visiting the concerning plants and asking what was the matter. Some of his more illuminating results may serve as illustrative examples.

A considerable number of significant changes of the incidence rate were due to approaching or ending holidays. As a rule the incidence rates begin to fall one or two weeks before the holidays. Immediately after the holidays they start at a high level and in the course of one or two weeks fall back to their habitual level. In some concerns this effect is much stronger than in other ones. It has been known for a long time that Sunday has a comparable effect. Every week the incidence rate is decreasing gradually from Monday to Saturday. This effect is not restricted to spells of short duration. It has been observed in the same degree for serious diseases of long duration.

In one concern the incidence rate was, against the general rule, particularly high in the summer months. This concern manufactures a product of which large quantities are sold in the summer. Keeping large stocks is expensive. So the concern has accepted the policy of taking from May to August every worker it can get. Then the acceptance of workers is stopped and a high labour turn over soon reduces the manpower to the level desired.

In September and October 1957 there was a great epidemic, mainly of influenza. Dr. Ekker subtracted for every concern the habitual level of the incidence rate in these months from the observed incidence rate over the epidemic and considered the difference as the part due to the epidemic. There was a strong correlation, that is, the parts due to the epidemic are roughly proportionate to the habitual level. Apparently the specific organisms involved are not the only agents responsible for the increased absenteeism.

Finally consider the following list of diagnoses and durations (in brackets) of the spells from January 1957 to April 1958 of *one* girl out of forty, working at a branch establishment of a great concern of department-stores:

Unknown (1), psychoneurosis (2), accident (5), psychoneurosis (4), not recorded (1), acute diseases of respiratory system (8), menstruation (1), acute disease of respiratory system (7), menstruation (1), influenza (10), menstruation (1), menstruation and psychoneurosis (4), influenza (3).

One would probably conclude that this girl is none of the healthiest, either physically or mentally. In her little population, however, she is quite an average girl. Her personal incidence rate is near to the very high average of 8 per man-year, her diagnoses are the prevailing ones. It is not likely that the small population of 40 girls is the result of negative selection. The directors are not dissatisfied with the girls, except for their high incidence rate. The list above should be considered as an average response to an unfavourable environment.

The medical diagnoses labelled to spells, are no predominant clue to the multitude of interacting and perpetually changing factors that govern the presence-absence balance of a worker or a concern. The gap between "diagnosis" and "cause" is much wider in the case of spells than in the case of deaths.

Some epidemiological aspects of tuberculosis in industry

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The campaign for combating tuberculosis, carried out by the Philips tuberculosis dispensary, covers about 80.000 people, namely the employees of the Philips factories together with their families, at Eindhoven.

From the very beginning, more than 25 years ago, the basic principle has always been early diagnosis and early treatment. This principle involves intensive casefinding, not only of new cases, but also of relapses. In our opinion early diagnosis of relapses is even of more importance than the detection of quite new cases.

Our methods of case-finding are:

1. Periodical examination (once in 2 years) of all employees, by means of fluorography. This examination is compulsory for the workers, and is laid down as such in the collective labour agreements. Suspected cases are admitted to the dispensary.
2. Frequent follow-up examinations at the dispensary of all cured patients. Frequency of these examinations is 12-6 times a year during the first 2 years after recovery, and later on 2-3 times a year. By this method we find about 90% of all relapses, which at their out-break in the great majority do not show any clinical symptoms or suffer from any complaints. This follow-up refers also to the so-called observation-cases: cases, which do not show any clear sign of activity, nor of inactivity. Mostly they have passed already their active phase without any clinical symptoms or signs.
3. Examination of patients admitted to the dispensary by the family-doctor. This is a group of patients who show more or less clinical symptoms or signs which might have a relation to tuberculosis. Our experience is, that in this group a much higher percentage of lungtuberculosis is found than in a group of apparently healthy people. Actually about 50% of all new cases of lungtuberculosis (relapses excluded) are coming from this group, admitted by the general practitioners.
4. Examination of contacts of cases of active tuberculosis. This group of contacts refers not only to the family and near relatives of the patient, but also to the colleagues of a sick employee.
5. Pre-employment medical examination of the applicants, which includes a fluorescopy. As a rule cases of cured tuberculosis are accepted, provided suitable work can be found for them and the risk of relapse does not exceed a certain degree.

The total number of X-Ray examinations is about 30,000-35,000 a year; this means in a group of 80,000 people an X-Ray index (as we call it) of about 400 lungexaminations per 1000 people a year.

A general survey of the course of tuberculosis-morbidity is given in *table 1*. There is an increase of the morbidity during the war, and a decrease after the war, whilst there is a nearly constant low level during the last few years. Whether this level will maintain itself for the next years or will proceed to a lower one, we do not know, but it is possible, that we have already reached our limit. Our group of population is not a fixed one: every year a certain percentage is leaving, and another percentage of people is coming in, with their tuberculosis. This out- and inflow of tuberculosis might prove to be a barrier to a further decrease of morbidity. We will have to come to a further study of this problem.

The observation-cases do not show such a fast and strong increase or decrease during war-time and afterwards as we see in the active tuberculosis. We can imagine that the tuberculosis disease, especially the post-primary tuberculosis, the phtisis, springs from a general bottom, which is formed by the number of positive reactors to tuberculin. Un-

Table 1 - Frequencies (Philips, Eindhoven)

Year	Active cases (new cases + relapses)		Observation cases (new cases)	
	No.	$^0/_{00}$ of Philips-population	No.	$^0/_{00}$ of Philips-population
1936	101	2.24	59	1.31
1937	125	2.30	93	1.72
1938	69	1.28	74	1.35
1939	73	1.33	48	0.87
1940	67	1.22	42	0.76
1941	82	1.34	50	0.81
1942	163	2.69	48	0.73
1943	171	2.47	82	1.18
1944	204	2.71	86	1.14
1945	161	2.59	71	1.15
1946	149	2.15	76	1.09
1947	155	2.11	73	1.00
1948	137	1.86	76	1.03
1949	90	1.24	44	0.61
1950	81	0.99	40	0.49
1951	61	0.75	37	0.45
1952	56	0.79	21	0.29
1953	45	0.64	15	0.21
1954	46	0.61	20	0.26
1955	46	0.57	21	0.26
1956	47	0.60	16	0.20

favourable social circumstances promote the proceeding of the disease from this bottom, but in the same time promote changing of lesions from low activity to high activity.

Thus the increase in the observation-cases will comparatively be less than in the active cases; on the other hand the data after war-time till about 1950 show that the gradually improving circumstances have influenced at first the incidence of active cases, and approximately 1 year later also the observation-cases.

Table 2 - Methods of case-finding

Year	Active cases of lungtuberculosis (new cases + relapses)				Observation-cases		
	No.	Family-doctors %	Dispensary %	Mass-examination %	No.	Family-doctors *and* dispensary	Mass-examination
	1	2	3	4	5	6	7
1944	204	39	47	14	86	53	47
1945	161	32	40	28	71	44	56
1946	149	39	50	11	76	50	50
1947	155	33	48	19	73	37	63
1948	137	37	49	14	76	37	63
1949	90	33	56	11	44	48	52
1950	81	28	55	17	40	32	68
1951	61	29	54	17	37	43	57
1952	56	30	38	32	21	33	67
1953	45	24	60	16	15	7	93
1954	46	24	41	35	20	25	75
1955	46	30	52	18	21	14	86
1956	47	34	59	7	16	25	75

Table 2 shows the significance and value of different methods in casefinding. From all the active cases (new + relapses) about one half is found by the dispensary (examination of contacts and follow-up of recent recovered cases), about 30-35% by the general practitioners (cases, showing clinical symptoms which draw attention to tuberculosis),and about 15% by mass-X-raying. Diagnosis of the group admitted by the family-doctors has to be confirmed by X-ray-examination at the dispensary; the first selection of suspect cases however is made on clinical basis by the general practitioner. From the observation-cases a gradually growing major part is detected by mass-X-raying.

Table 3 - All cases of lungtuberculosis, degrees of activity

Year	No. of cases	Active cases		Observation-cases (without signs of activity) %
		with clinical symptoms %	without clinical symptoms %	
1944	290	28	33	49
1945	232	22	28	50
1946	225	30	33	37
1947	228	22	32	46
1948	213	25	31	44
1949	134	22	37	41
1950	121	19	36	45
1951	98	18	33	49
1952	77	22	27	51
1953	60	18	45	37
1954	66	17	29	54
1955	67	21	36	41
1956	63	25	44	31

Combining from table 2 the active and observation cases, and dividing them in different degrees of activity, we see from *table* 3 that about 25% show clinical symptoms, about 35% show activity without clinical symptoms, and about 50% do not show signs of activity at all. (We must keep in mind however that mass-X-raying in our group of population covers only about 30% (the employees) of the whole group; therefore the figures in this category do not give a quite correct picture of the epidemiological situation).

So from all detected cases of lungtuberculosis, nearly one half shows more or less signs of activity, and only a minor part shows clinical signs and symptoms of activity. The question arises, whether there is a difference between these categories from an epidemiological point of view. Regarding infectiousness there undoubtedly is.

Our cases with clinical symptoms or signs of activity (referred to the dispensary by the family doctor) showed an average percentage of 25% of open tuberculosis; the active cases without clinical signs (contacts, relapses found by follow-up examinations) showed 45% of open tuberculosis. So these cases are of more epidemiological importance than the other ones. But if we consider only the new cases (excluding the relapses), we do not see any difference between the two categories. So the relapses contribute greatly to the risk of infection. This involves therefore the necessity of a long-term-follow-up of all cases with a great chance to relapse, and of their close contacts. A small percentage of the observation-cases shows intermittent production of some few bacilli, and such cases certainly are far less infectious than the active cases.

Not only infectiousness however, but also frequency of relapse has to be considered.

From *table* 4 can be seen that the differences in relapse-percentages in the active cases of post-primary tuberculosis (phtisis) and in the observation-cases are small and hardly of

statistical significance. This fact is of great importance for the organization of a well-balanced case-finding program.

We also observe a decreasing frequency of relapses in the recent years. So as regards relapses case-finding of active cases and of observation-cases is of nearly the same importance.

Table 4 - Relapse-rate in cases of active lungtuberculosis and in observation-cases after 4 years of follow-up

Calender years	No. of cases of active lungtuberculosis (phtisis)	No. and % of relapses after 4-years of recovery	No. of observation-cases (phtisis)	No. and % of relapses after 4 years of follow-up
1930-1939	119 = *100%*	56 = *47%*	84 = *100%*	31 = *37%*
1940-1944	169 = *100%*	59 = *31%*	136 = *100%*	36 = *26%*
1945-1950	225 = *100%*	42 = *19%*	181 = *100%*	31 = *18%*
Total	513 = *100%*	157 = *31%*	401 = *100%*	98 = *22%*

Summarising these data, we may say that most of the active cases will be detected by paying attention to all clinical symptoms which might have a relation to tuberculosis, but above all by "focussed case-finding" in people who are recovered from tuberculosis, whether the active phase has been detected and treated or not. These last-mentioned cases (observation cases) for the major part will be detected by periodical mass-X-raying. In our opinion the great importance of mass-chest examination is to be seen first of all in the spotting of the group of observation cases, from which future activations might be expected.

For the detection of active cases the interval between the examinations (about 1-2 year) is too long in comparison with the speed in which active t.b. will develop as a rule, to offer a good chance for a real early diagnosis.

Consistent use of these methods of case-finding will help us considerably in controlling the tuberculosis-epidemic. The results will be a decreasing morbidity and relapse-percentage (as recorded already). Furthermore by being able to apply all kinds of therapy in the very early phase of development of the disease, lethality and therefore mortality, can be greatly reduced.

Table 5 - T.B.-mortality per 100.000 of the population

Years	Philips population	The Netherlands	Years	Philips population	The Netherlands
1936	23	50	1947	17	37
1937	28	48	1948	4.5	28
1938	28	45	1949	4.5	24.5
1939	19	41	1950	0.–	19
1940	19	44	1951	3.5	16
1941	10	60	1952	5.5	12.3
1942	17	61	1953	1.8	9.3
1943	14	70	1954	1.6	7.5
1944	39	75	1955	4.6	6.7
1945	23	86	1956	0.–	6
1946	7	47			

Table 5 shows the course of t.b.-mortality in our population group compared with t.b.-mortality in the Netherlands. The lower level of the crude mortality-rate in the Philips group is partly due to the somewhat higher social level of this group, but undoubtedly for another important part to intensive case-finding.

A remarkable fact is the continuing decrease of Philips-mortality during the first years of the war, whilst the total t.b.-mortality from the very beginning shows an increase. This is mainly due to early diagnosis and early treatment of relapses, resulting in a delay of progression of the lesions.

This barrier has been broken through only during the last year of the war. Afterwards the Philips mortality from t.b.-approaches almost to zero. Even on this low level, Philips-mortality as an average of the last 5 years, namely 2.5-3 per 100.000, is about 3 times as low as the general dutch t.b.-mortality, which gives an average of about 8 per 100.000 during the last 5 years.

Are we already at the limit with our methods as described above which have been such a success in controlling t.b.-mortality and reducing t.b.-morbidity? We nearly have conquered the first, but the problem of t.b.-morbidity remains and is a very comprehensive one. In our favourable social circumstances exposure to infection plays a minor role, whereas susceptibility to development of the disease is the major factor. Yet the main part of our t.b.-campaign is directed towards prevention of infection and to case-finding of the already existing disease.

Can we develop methods to prevent infected people to get sick, and would it be desirable to eradicate all possibilities of infection? Only a very small percentage of infected people contract the disease. About 60% of the Dutch population above the age of 15 years show a positive tuberculine reaction, but every year only 2-3 $^0/_{00}$ of the positive reactors will show more or less signs of active disease, and another 1-2 $^0/_{00}$ will be found as observation-cases.

B.C.G.-vaccination will prevent about 80% of primary-tuberculosis, but the incidence of primary tuberculosis in our country is decreasing so fast that it is questionable whether vaccination, provided it could be applied to all children, would be of considerable help in controlling this disease. A programm of mass B.C.G.-vaccination in the group of Philips employees, carried out during 5 years (from 1949 till 1954) contributed only a very small part to the reduction of morbidity. It had to be stopped because of the small but undeniable risk of serious damage, which has been recorded by Wallgren and other Scandinavian authors. However, B.C.G.-vaccination has proved its great preventive value for close contacts of infectious cases of tuberculosis. In this group we therefore continue using B.C.G. Prophylactic use of antibiotics also seems to be worthwhile in a number of cases; we apply antibiotics to prevent outbreak of relapses, and in children and young adults, who have been exposed to serious infection, even when their tuberculin reaction has not yet been converted.

Prolonged antibiotic treatment in active cases, together with resection therapy certainly will reduce the frequency of relapses.

In conclusion we may say that there are means already available for further prevention of the disease and further reduction of morbidity. One of the most difficult problems, whether and by what means the basis of tuberculous disease, formed by the group of naturally positive reactors, could or should disappear and should be replaced by artificial infection, requires further intensive study.

Anyway, our morbidity- and mortality-figures show clearly that the eradication of tuberculosis-morbidity must be pursued and that the eradication of tuberculosis-mortality can be obtained within a rather short time by the continuous and strict application and organization of all means, which lead to early diagnosis and early treatment.

The Neurosis Problem

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These views on the neurosis-problem are presented on behalf of our recently created working-unit on this subject, including among others Dr. Hamburger, psychiatrist, Dr. M. J. W. De Groot, medical statistician, Dr. J. De Groot and Dr. Van Alphen de Veer, occupational physicians of the Royal Steel- and Ironworks at IJmuiden and of the Philips-factories at Eindhoven, and Dr. Lahr and Dr. Den Haan, general practitioners at Leyden, Miss Oorthuys and Miss Van Harmelen, social workers of the University Hospital and the outpatient department for internal medicine of the Leyden University.

This preliminary report is intended as an illustration of approaching a public health problem by means of a joint effort of a working unit composed of both clinical workers and public health officials.

In his paper Dr. Knowelden has put amongst others two questions: how to prevent and before all: what to prevent. He has alluded to the descriptive task of epidemiology applied to one disease or a small group of diseases. It is only then that we can understand the influencing factors or the cooperative factors or conditions that are playing a role and that bring the individual in a situation of risk. Dr. Alice Stewart introduced that word in the discussion and I must say it is very adequate for the epidemiologic study of neurosis and kindred disorders where no specific condition is exactly known, comparable with a specific condition like the tubercle bacillus in tuberculosis.

Dr. Breslow in his turn has spoken of four phases of epidemiological research. I suppose that in our neurosis working-unit we are dwelling around phase I, the retrospective investigation. Probably also a beginning has been made with phase II, confirming hypotheses, since we make a follow-up of our studied cases.

It is not our intention to comment now on neurosis as a problem in the psychotherapeutic situation, in which we have to deal with neurosis more or less in a limited and classical sense, more or less differentiated from other psychiatric diseases in terms of a combination of psychic qualities within the personality.

In our efforts for readaptation of the patient we agree on how to solve the therapeutic difficulties. As a rule we realize this readaptation by changing certain entities within the personality leaving it to the patient to rehabilitate himself with his newly gained attitude to the world around him.

Today on the other hand we are confronted with the problem of neurosis on a nation wide scale, its structure and extension. The application of epidemiological methods to the study of this form of mental disorder is rather confusing.

For the purpose of counting in epidemiology, the countable units – or for an inventory for needed therapeutic facilities – the old categories hysteria, psychasthenia, neurasthenia are definitely insufficient. These syndromes have changed since the time those names were given. And moreover our knowledge about kindred forms of neurotic disorders has been enlarged. We know that not only the neurotic in the psychotherapeutic consulting room is suffering from inhibitions and outbursts of emotions from unpremeditated compulsory behaviour and from senseless suffering caused by his inability to deal with his feelings on the one hand and reality on the other hand. This inability is a result of the interplay of his emotional life history and his innate abilities. We know that many who never come to the psychiatrist, involved as they are in an endless struggle against reality, find other less adequate ways of seeking help and cure at the operation table, in physical therapy, by the gynaecologist, by the dermatologist, and at all kinds of outdoor departments. How many of them are the "crux medicorum" of the general practitioner who is burdened by them. But notonly with the medical profession, also in court they manifest themselves, and at social

welfare agencies and at their workshops. And then there are many really somatic patients with that considerable amount of so-called or real "neurotic", emotional complication superimposed upon their somatic illness. And last but not least there is the real psychosomatic patient to whom emotional (neurotic?) factors caused somatic damage. For this purpose our classic neurosis nosology is insufficient. So it seems to us that first of all the basis of our diagnosis has to be enlarged.

What at least should a diagnosis tell us about the patient for our world-wide purpose when dealing with neurotics and kindred patients? And the preliminary question, what is a diagnosis?

Diagnosing is referring the symptoms to assumed fundaments and theories lying at the bottom of our conceptions of normal and abnormal functioning. This is not always done consciously by the diagnosing doctor. But as far as he reduces a case by bringing it in connection with a general accepted system of conceptions about cause or (better) conditions, course, termination and obduction, he is diagnosing, although in a onesided way.

In modern psychiatry a broader way of diagnosing was introduced by Kretschmer and Birnbaum called *multidimensional diagnostics*.

We follow this principle when for the purpose of identifying our patients we try to classify them in the well-known traditional classification of nosological psychiatric entities (Kraepelin).

But at the same time we try to understand the symptoms as coming from a character-background seen as a structured organization at a certain moment in a given situation. I am referring here to the psychodynamic, topic and economic conceptions of psychoanalysis.

We try to bring the symptoms in relation to a cross-section through personality structure. In which way we ask ourselves, is the dominating dysharmonia of the personality expressed in a constellation of instinctual drives, character, constitutional temperament, intelligence, psychomotorics?

Sometimes it is possible to understand our patients in the way anthropological psychiatry is trying to teach us. It is understanding the other by approaching him from our own existence, a subjective way of diagnosing.

But here we come to a field of special interest to our working group. We ask ourselves what are the human relations the patient lives in. Or put in another way: how is his normal conflictuology? What kind of personal tensions, family conflicts and grouptensions in work, street and other environment are working on him and influence his pathologic state adversely?

Or on the other hand how are his very peculiar group relations belonging to normal human existence even holding him in balance? Furthermore, to what extent is the patient himself the motor of pathologic grouptensions? All this is condensed in the question: *what is his social role*?

In order to be able to understand the patient better and to know how to deal with him, we need a precise description by the visiting social worker of his social and economic circumstances and his behaviour in his work, in his leisure, in his hobbies, in his family life, towards his wife and children, and in his social, cultural and practical occupations and so on.

As to this whole field of human relations and social circumstances we in our Institute are convinced that the patient expresses his mental illness in his clinical as well as in his social behaviour pattern. It is our opinion that there is no essential difference in value nor in comprehensibility of both fields of expression.

There is still another aspect which we have to take into account when diagnosing a patient.

I mean the findings of clinical chemistry and of electrophysiology of the brain. Further, we have to pay attention to the peculiar general physiology of the patient as well as to his patho-physiology or even to his limitations by organic invalidity or illness.

In this broad and multidimensional way we are in fact diagnosing the patient in his unique constellation and not merely labelling him. Thus *our diagnosis is a short résumé in multidimensional terms.*

How have we organized our work?

Four occupational physicians of two big factories viz. the Royal Iron- and Steelworks at IJmuiden and Philips at Eindhoven bring in their problem cases, the so-called "neurotics". The same is done by two general practitioners. These doctors, mostly a number of them together at the same session, present their patients to a team consisting of one specialist on internal medicine, three psychiatrists, one psychologist, two medical statisticians and two or three social workers.

Most patients are examined by either the general practitioner or the occupational physician and by a social worker during a visit at the patients home, as well as by the psychiatrist who has at least had one interview of more than one hour.

Every patient is finally invited to fill in the Maudsley medical questionnaire revised by Heron indicating the factor of neuroticism.

During the staffmeeting a short multidimensional diagnosis is made according to the diagnostic principles enumerated before and by general consent. This is laid down in the files as a conclusion.

Plans are made for readaptation (rehabilitation) of the patient and advice is given to the doctor and the social worker who deal with the case. Sometimes specialist help is required.

So far this is all traditional though systematized and multiprofessional diagnostic and therapeutic work in its broadest sense. But besides all this we distinguish ourselves from traditional work by quantifying in a simple 7-step scale the way in which the patient is maladapted to himself (somatically or psychically) to his family, to his work, to his further social cultural environment.

So we have a scaling of the intrapersonal and interpersonal relations and the way in which the patient is adapted to them. In future we will compare this with a scoring list of symptoms of maladaptation in every domain of our diagnosis. And we will try to test out the validity of this scoring list of maladaptation in order to be able to know something about adaptation or not and modalities of adaptation by the simple way of filling in a list without broad and time consuming diagnostical activity, multiprofessional, and in team.

So, besides our aim of making in a first pilot study an inventory of morbidity patterns, we intend to develop a kind of rating scale for various degrees of maladjustment-aspects in the total picture of its presentation. On the other hand a first concept of a scoring diagram has been composed by Dr. Hamburger, Dr. M. de Groot and myself by putting clearly to ourselves what kind of information one needs for an integral knowledge of personality in his intra- and interpersonal relationships with special respect to pathology of adaptation, somatically, psychically and socially. Special technical problems as to reliability and validity of separate items on the scoring list are still to be worked out.

A second difficulty refers to the variability in judgment and interpretation between and within the members of the group, since it seems impossible to restrict ourselves to a very set of objective, well-measurable data. But since Dr. Alice Stewart has reminded us of Dr. Snow and his pump and that he was right in spite of his terrible inaccuracy of method we here in our Institute still have some hope. But of course, we don't expect to overcome

on short term the huge amount of problems we doubtless will encounter in our trial to quantify the various modalities and degrees of maladjustment, but since we started the job we don't hesitate to go forward.

Anyhow besides this special aim of developing a scoring system for pathologic adaptation in several modalities, we think that we will gain a new insight in patterns of disease and maladaptation on a pathologic or on a normal basis by our collaboration with the occupational health services of two factories and with two general practitioners. Many of these patients were in the past thrown together in the much too big dustbin of "neurosis".

After some time certainly we will notice the reiteration of occurring cases brought in by the doctors and their social workers. In this way, by a subjective selection of a number of "problem cases", in our pilot study we will first of all come to a diagnostic inventory and to an insight in needed therapeutic facilities in its broadest sense: medical care or psychotherapy or social work or public health or organizational or legal measures. Secondly we hope to develop gradually an insight into the relative weight of the various syndromes that present themselves, being a rough outline of morbidity.

Finally two examples may further make our conceptions clear:

CASE I

A man of 32 years, married and living in his family, 2 children and working in a hardwareshop for several years where he had a friendly relationship with his boss. When this shopowner died and our patient had to look for another job, trouble began. He could not re-establish such a protective relationship immediately and in several jobs which he tried he became more and more panicky. He came to the general practitioner with diarrhoea and other intestinal complaints. He seemed to suffer from fears. Somatically nothing could be found. Psychiatric interview showed a pseudo active intelligent man with no serious neurosis but with some infantile character traits.

The social worker could not report anything special. After re-establishing a new affective relationship in a suitable worksituation, his complaints disappeared.

This is an example which could possibly be interpreted by calling it a state of psychosomatic disorganization caused by social factors. The stamp "neurosis" however would be very unsuitable for this case as a base for therapy or rehabilitation.

How have we diagnosed this patient? First of all we recognized him as not belonging to any of the classical nosologic entities of psychiatry. His personality structure on the other hand was not unintelligent but emotional and immature. Psychodynamically during two interviews, where good affective contact was established, it was not possible to see this patient as a serious neurotic personality, his personal subjective world being a world of good fellowship and being brotherly together. Up till the time of the collapse of his worksituation our social worker could not find anything serious in his life history.

Then suddenly calamity arose. Several examinations in the field of internal medicine were performed and finally he was sent to the psychiatrist. To conclude: It seems to us that two relevant features prevail: the underlying immaturity, not manifest in normal circumstances, and secondly the sociogenic borderline situation he came in and that caused his illness. I presume that the severity of the symptoms stretched over such a long time, the only gradual recovery from this period of illness as an effect of re-establishing good workrelationships, justify our conclusion that we had to do with a morbidity pattern. His adaptation during his illness was very bad. Full intra and extra personal maladaptation, somatically and psychically, was combined with maladaptation as a working man, and with disorganization in his family life.

CASE II

A married man of 56. The social worker describes this man and his family as follows:

Rather primitive large family with working children, good family relationships although the last 2 years the whole family is in uproar in a peaceful way, when patient suffers from pains in his stomach. This has an exaggerated touch.

He is further coughing as a result of frequently recurring bronchitis especially in wintertime. This started several years ago. There is a slight emphysematic thorax and the outpatient clinic of the department for internal medicine of the University of Leyden could not find anything more than a slightly increased acidity in the stomach.

Some 2 years ago by some mysterious decision patient was declared unfit for work and got his disability pension. Without doubt this has had a bad influence on his morbidity-state.

Psychiatric interview brought to light that in the past this man has been always very proud of his physical strength and his healthy body and that his actual state of invalidity, of which the somatic examination could only find slight symptoms, was constantly present in his mind. He was emotionally hurt by it.

A special feature was that the patient did not keep it to himself but on the contrary embarrassed everyone, particularly his family. This seems to be a kind of compensation for him. Psychodynamically it was not possible to interpret these mechanisms either as neurotic nor as psychopatic. They were primitive and narcistic. His temperament is indolent, his intelligence normal.

This raises the question whether one could explain his emotional breakdown and his luxurious somatic complaints by a shift in mood during involution. Or as a "forme fruste" of involution-depression such as one sees so often as a basis for changes in attitude, e.g. pathologic drinking habits developing at that age, etc.

Involution depressions of this type certainly occur rather frequently but at the same time I hold the opinion that one has to differentiate such genuine forms from similar syndromes but with another mechanism at the bottom. In this case for example one has to ask whether there is not a considerable decrease of ventilatory capacity of the lungs. The only hardly conscious experience of it must have had a considerable effect on this narcistic man, so sensitive to limitations of his physical abilities. We have asked our lungphysiologist to examine this man and to inform us about him.

Of course we will further look for an early sclerosis of the brainvessels as a cause for the changes in mood of this man. Anyhow to conclude: his adaptation was a bad one, psychically, somatically, in his worksituation and in his social situation. Only within his family it was more favourable although through special positive factors within this family not stemming from the patient himself. The case was presented to us as neurotic but after our explanation I hope we agree that this diagnosis is not covering the real state. It is probably better to characterize it as a gradual collapse of a peculiar personality caused by an increasing limitation of his physical or physiological abilities.

Occupation and psychological disorder

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My aim is to describe the collection and analysis of some data on the interaction between occupation and psychological disorder. I use the term "interaction" advisedly because the relations between psychological disorder and job are very much a two-way business with each influencing the other. In war, these interactions are seen at their most dramatic and acute. In the Royal Air Force, for example [1], I was concerned with the detection and measurement of the effects of the psychological stresses of air warfare on both the efficiency and the health of bomber crews.

During a typical bomber sortie, two psychological stresses were operating: the acute anxiety of contact with the enemy defences and the cumulative "fatigue" coming on at the end of a long flight. The relative effects of these two types of stress on occupational skill or function were measured by noting the arithmetical errors made by navigators at different stages of the flight. From such studies it became clear that the effects of acute anxiety, measured in these terms at least, is much more important than the "fatigue" effects of prolonged activity. A question of greater moment in the epidemiology of neurosis and allied conditions is whether such anxiety and fatigue can be related to bodily changes and, ultimately, to the risk of psychological breakdown.

Observations on the use of the oxygen supply apparatus showed how the fluctuations in one sign of emotional tension – the respiration rate – coincided exactly in time with the stages in the sortie at which action was at its most hazardous. But more important from the medical point of view was the long-term effects of these tensions on physique as well as on operational efficiency. Clinical experience with pilots and others who had broken down suggested that there were certain associated detectable changes in physical function. These included loss of weight and increasing inability to achieve binocular fusion of images when tested by the Livingston gauge. Some field observations were made on bomber crews at different stages of the prevailing operational tour of 30 sorties, against German targets. The body height and weight in large groups of men in the R.A.F. Bomber Command were measured at one moment in time and then grouped according to their operational experience. When the mean values at different stages of the tour were plotted out, the constant level in mean height among men at different stages showed that there had been no obvious selective elimination of men of slighter physique. There was, however, a small but definite loss in weight in the earlier stage of the tour but not thereafter. Since there was no selective loss of the smaller men, this trend was unlikely to be an artefact. Again, there was *no* such fall observed in similar observations made in the training squadrons at the same time.

Psychological stresses can thus have a measurable effect on occupational function and personal physique. How may this be extended to clinically evident disorders? Here we can use the first of the four methods of data collection which can be used in such circumstances: the *special morbidity survey*. At this stage of the war, we set up a reporting system whereby all members of flying crews who developed symptoms and signs severe enough to demand referral to a psychiatrist were notified to the Air Ministry. These cases were then divided up according to the man's job, operational flying experience and the Command in which he served. They were then related to the aircrew population which was classified in the same way. The relative risks of neurotic breakdown in different groups could thus be quite readily calculated.

When, for example, we compared the rate of breakdown at different stages of the operational tour of 30 bomber sorties, it became quite clear that the trend in clinical disease

followed the indications of periods of maximum stress given by weight changes; and it is interesting to note that minor illnesses of all kinds reflected, if rather dimly, the same general trend. Like the trend in weight, there was no suggestion of a change in the later stages of the tour.

Three factors may be operating, (1) the environmental stress of air warfare, (2) the selective elimination of those constitutionally disposed to neurotic illness, and (3) the cumulative effects of fatigue.

Quite clearly, there was no indication in these data that within a tour limit of 30 sorties, cumulative fatigue was important. On the other hand, there was good reason to believe, from this and other evidence from this epidemiological survey, that the other two factors were decisive. When, for example, we compare the incidence of neurotic breakdown in the various Commands of the Royal Air Force in 1943, the rates (which were highest in Bomber Command based in the U.K.) were quite obviously related to the danger and intensity of air warfare rather than to the extra stresses involved in separation from home in the Middle East forces.

I extended this approach [2] to the measurement of environmental stress effects by relating the incidence of neurosis in individual squadrons to the casualty rate suffered by these particular formations. It was significant that a burst of heavy casualties was followed at once by a crop of breakdowns and a month later by a crop of cases of venereal disease.

Although this is now an old forgotten story, these general ideas and methods are readily applicable to the problems of neurosis in peace-time industry [3].

We can use the second form of data (the *routine absence statistics*) to compare the incidence of mental and psychoneurotic illness among postmen working in four groups of areas of increasing density of population. There is a clear association between the postman's life in the larger cities and his liability to sick absence because of neurotic illness. In view of the long suspected association between psychological disturbances and alimentary upset, it is interesting to note that the same gradient appears in the incidence both of peptic ulcers and the group of "all other digestive disorders."

Again, in the Air Force at war, we compared the incidence rates according to the job done in the bomber crew. When all were subjected to the same external risk, the breakdown rates were highest, not among pilots who held the most responsible posts, but among the air gunners. Air gunners were not subject to the same long and gruelling training as the pilot. Selection as well as operational stress thus determines the rate of breakdown among men doing different jobs in the air.

We can use the data published by London Transport Executive to translate this approach to the crews of peace-time London's buses and trains and the technical and clerical staffs who help to keep them running. The pattern of age-standardised absence rates (expressed as the average number of days lost per person per year) because of either functional nervous disorders or diseases of the stomach and duodenum by men and women doing various jobs in London Transport falls into three groups. On one side there are the crews of buses and trains who have relatively little neurosis but much absence from work because of digestive disturbance; on the other hand, the women clerks, married and unmarried, are less prone to absence because of digestive upset but more disabled by frank neurosis. Between lie the workshop staff, the technicians and the clerks whose sick absence pattern is the same as the other males but with rates nearer to the females. Both these latter groups of men and women have static rather than mobile jobs. Within each male group, however, the gradients for both types of illness are identical: the bus conductors, for example, suffer more absence from both neurosis and digestive disorder than the less harassed and perhaps more placid train crews in the Underground.

The age pattern of both neurosis and digestive disturbance again are broadly similar

with peaks in early adult life among the married women, in the forties for the unmarried women and in the fifties among the men. They might thus be looked on as different responses to the difficulties and tensions of life at work and outside it; and these pilot studies serve to underline the relevance to mental health of city life, the selection of men to jobs and the epochs of particular strain in the lives of working men and women.

The third form of morbidity information comes from statistics of *admissions to mental hospitals:* and our Registrar-General [4] has just published an analysis of the social and occupational background of patients admitted to British hospitals. Rates for first known admission have been calculated for the 5 social groups into which our population is divided at each Census: professional, managerial, craftsmen, semi-skilled and unskilled.

As far as schizophrenia is concerned, the ranking of hospital admission rates follows the downward intellectual gradient from professional to labouring men. But in manic-depressive psychosis, there is a suggestion of a rise among the professionals. The errors in the more detailed analysis by job are considerable; but, here again, the overwhelming effect of selection is obvious in the low rates for the supervisory groups in industry and the relatively high ones for those who have drifted into the personal service as barmen, kitchen-hands, etc.

The final measure of mental ill-health comes from the *mortality data* of the Registrar-General. Of all the mental disorders, probably depression ending in successful suicide is the only one where mortality data give much evidence of relative frequency in different population groups. One illustration will serve to emphasise a fundamental point in the interpretation of the geographical distribution of disease in general and suicide in particular. In the course of a study of the health of coal miners in our country, we found that, as a group, miners have a low suicide rate. In view of the gruelling process of selection which the hard and dangerous job entails, this is hardly surprising. More interesting, however, is the difference between coal mining areas of Britain. During the economic crisis of the 1930s large numbers of young men left the mines in the most depressed areas. Now, in the 1950s, the effects of this migration are evident in the positive correlation between the proportion of men who have left the particular area and the death rates, e.g. from bronchitis, among those who remain. Clearly the physically fittest have left the area and the industry. On the other hand, quite the opposite occurs in suicide where the death rates for this cause are lower in the areas from which migration has been greater. Equally obviously, the migrant groups may include the physically fitter men; but they also include the mentally unstable.

In setting out these simple methods using crude data, I have tried to suggest the need in this developing field for a dynamic rather than a static concept of the behaviour of psychological illness in differing occupational groups. Certainly, contemporary environmental circumstances do appear to influence the current incidence of neurotic illness; and those external stresses may be reflected in measurable physical changes. But the interpretation of these current rates of the various indices of psychological disorder in different occupations must take into account the continuously changing effects of selection – either by initial recruitment or subsequent wastage – and the ebb and flow of men through an industry as its economic circumstances vary.

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The post-hospital adjustment of chronic mental patients

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Until recently, it was established that once a patient had stayed for two years continuously in a mental hospital his chances of discharge in any subsequent year were low (Kramer et al., 1954, Carstairs et al., 1955). This situation may now be changing.

Two recent reports from America (Brill and Patton, 1957, Kramer and Pollack, 1958) show that in the year 1955-56, the year in which the use of tranquillizing drugs became widespread, the total number of patients resident in State Mental hospitals declined, in reversal of a long-established trend, and the former of these papers showed that in New York State this could largely be ascribed to an increase in the number of discharges – an increase which was especially marked for discharges of patients with over two years' stay in hospital. These papers did not, however, indicate the level at which patients were functioning after their discharge from hospital.

In most cases, when a psychotic patient is discharged after a prolonged stay in hospital, he is not completely recovered, but carries at least some residual disability. His remaining in the community will depend partly on the nature and degree of this psychiatric handicap, and partly on the social environment to which he returns.

The present study was designed to ascertain the outcome of long-stay patients discharged from mental hospital and to look for factors in their history and in their subsequent social experiences which were associated with their level of adjustment in the community.

METHOD OF INVESTIGATION

1. *Selection of cases*

The population consisted of all those male patients who were discharged by any means from 7 mental hospitals in or near London between July 1949 and June 1956, and who fulfilled the following criteria:

(1) subjects of the United Kingdom by birth;
(2) aged between 20 and 65 on discharge;
(3) had been in hospital for 2 years or more before discharge;
(4) not known to have gone to an address outside the Greater London Area.

2. *Selection of informants*

Whenever possible the primary informant was the housekeeper of the domestic group to which the patient went on leaving hospital. This was typically his mother, wife, or sibling, but in some cases his landlady. Where the patient had been living quite alone, he himself was interviewed.

3. *Follow-up interview*

An interview schedule was prepared covering 160 items, selected on the assumption that they might have a bearing on the patients outcome. The schedule was usually completed for each patient after a study of the hospital case notes and an interview with the primary informant lasting from 1-2½ hours. Sometimes more than one person was interviewed.

4. *Measures of outcome*

For the purpose of analysis, each patient's outcome was assessed in terms of the following criteria:

(A) *Duration of discharge period:* 'Success' (S) was defined arbitrarily as staying out of hospital for at least one year; re-admission for more than one month during the year following discharge was counted as 'failure' (F).

This is an abbreviated version of a report with the same title, by G. W. Brown, G. M. Carstairs and G. G. Topping, to be published in the *Lancet* in July 1958: it is here reproduced by permission of the Editor of the *Lancet*.

(B) *Level of social adjustment:* All patients counted as 'successes' were rated by means of a scale of social adjustment, in which one point was given for each of 3 items:

a) being gainfully employed for 5 out of the last 6 months in the first year of discharge;
b) being able to look after himself with regard to appearance, dress and use of money;
c) showing adequate interpersonal relationships – i.e. without gross disturbances such as violence, paranoid ideas or extreme withdrawal.

A score of 3 points rated: full adjustment,
2 points: partial adjustment and
1 or 0 points: poor adjustment.

From the records of the 7 hospitals, 240 men were identified who fulfilled the necessary criteria, and schedules were completed for 229 individuals (95%).

The diagnoses of the population studied are given in *table 1*.

Table 1 - Diagnoses

	No.
Schizophrenia	156
Depression	26
Epilepsy	18
Organic psychoses	10
Psychoneuroses	9
Mania	5
Diagnoses other than above	5
Total	229

If the population is then divided into two main categories 'schizophrenia' and 'other diagnoses' it can be further described in terms of the factors: specified in *table 2* (age, length of stay, first admission, marital status and condition on discharge).

Table 2

	Schizophrenia	Other diagnoses
Mean age (range 20-65)	39.4 yrs	45.0 yrs
Mean length of stay (range 2-30)	6.5 yrs	6.5 yrs
First admission (total adm. = 100%)	31.4%	43.8%
Marital status on admission: *single*	77.6%	42.5%
Discharged:		
against medical advice	31%	15%
recovered	14%	13%
relieved	65% } 100%	77% } 100%
not improved	21%	10%
Behaviour after discharge		
nearly normal	39%	45%
moderately disturbed	35% } 100%	36% } 100%
severely disturbed	26%	19%

Before assessing the patients' outcome, one would like to know as accurately as possible their mental state at the time of discharge; but in this retrospective study precise information on this point was not available. Some measure of the patients' mental state was however provided by the following observations:

(a) whether discharged on or against medical advice;
(b) whether recorded as 'recovered', 'relieved', or 'not improved' on discharge;
(c) a rating of the patients' level of disturbance of behaviour while living in the community one year after discharge, or just prior to readmission in the case of 'failures.' This was estimated on the basis of questions concerning ten specific features of the patient's behaviour, and was rated in three categories: 'nearly normal,' 'moderately disturbed' and 'severely disturbed.'

32% of the total population were 'failures' and 68% 'successes': percentages were comparable for schizophrenia and other diagnoses.

'Other diagnoses' had a slightly superior but nonsignificant ($p > 0.10$, 2 d.f.) distribution of social adjustment scores.

26% of the total population showed a very satisfactory or 'full' social adjustment (93% of these were rated 'nearly normal' in behaviour), while 22.8% made a definitely poor adjustment; 18.9% were intermediate between these two social adjustment categories.

The two indicators obtained from patients' case notes ('discharged against advice,' and 'recovered,' 'relieved' or 'not improved' on discharge) were both related to our criteria of outcome.

The rating of patients' level of behaviour was also correlated with outcome, both in terms of 'success'/'failure' and of social adjustment.

It is clear therefore that in evaluating subsequent relationships between clinical and social factors and the patients' outcome a first precaution must be to ensure that the relationship is not a reflection of the patients' differing levels of clinical state at discharge. In many of the following instances the above indices of clinical state at discharge have been used to partial out at least crude clinical bias.

The relationship of the *number of previous admissions* to outcome differs for the two diagnostic categories, schizophrenia and other diagnoses.

31% of the schizophrenics were first admissions, and only a small number (17%) had been in hospital three or more times before. This small category contained relatively more 'failures' (12 'successes' and 15 'failures,' $p < 0.01$) but showed no relationship with social adjustment scores.

In contrast, 'other diagnoses' had a greater number of first admissions (44%) of whom only 3 out of 32 'failed.' In this diagnostic group, the number of 'failures' increased significantly in the group of patients who had been in hospital before, compared with the first admissions (21 out of 41 of these patients failed, $p > 0.001$). Again no relationship was found with social adjustment scores.

For neither schizophrenia nor for the other diagnoses did the *length of key admission* bear any direct relationship to 'success'/'failure' rates. However, for schizophrenia those with 'poor' adjustment were mainly concentrated in those with less than 10 years' stay ($p < .05$): although trends are not marked, schizophrenics with longer stay in hospital had a slightly superior outcome.

Only 2 out of the 17 schizophrenics over 55 years of *age (at discharge)* 'failed.' Otherwise age bore no relationship to S/F either for schizophrenia or other diagnoses. With regard to social adjustment, however, the younger schizophrenics, aged between 20-34 years, were significantly more often found to be 'poorly adjusted' ($p < 0.01$) while 'other diagnoses' showed no such relationship.

Various measures of *pre-admission levels of social achievement* were obtained in the areas of employment and economic responsibility. Superior achievement was usually significantly

related to post hospital 'success' and to higher social adjustment scores. The relationships still remained when clinical state at discharge was taken into account.

The two most important factors in the *social experience* of a discharged patient were found to be:

(a) whether the patient worked and
(b) with whom he lived.

There was an important relationship between employment record and 'success' or 'failure' in staying out of hospital. 41% of the population worked for 6 months or more and of these 97% 'succeeded,' while of the 43% who were never employed, only 46% 'succeeded'. It is of interest that of the 89 'successful' patients who worked for most of the year, a third were rated as either 'moderately' or 'severely disturbed,' and many of the others had residual symptoms, indicating that the presence of psychotic symptoms was not necessarily a serious obstacle to their employment.

From *table 3*, it can be seen that schizophrenics who returned either to parents, wives or hostels, relapsed in the first year significantly more often than did those returning to other kin (mainly siblings) and lodgings. Those who did 'succeed' while with their parents had significantly lower social adjustment scores than patients living with other kin or in lodgings. Fewer living with parents were employed compared with the 'successful' patients living with their wives, with other kin or in lodgings.

Table 3 - Living group at discharge by S/F

	Schizophrenia			Other diagnoses		
	Success	Failure	Total	Success	Failure	Total
Hostel	6	7	13	4	7	11
Hostel (supportive)	1	—	1	4	3	7
Parental	55	31	86	8	8	16
Marital	7	7	14	16	1	17
Other kin (mainly siblings)	20	4	24	9	3	12
Lodgings	18	—	18	8	2	10
Totals	107	49	156	49	24	73

It was found that relatively more patients rated 'not improved' on discharge went to stay with their parents, or in hostels; but these differential 'failure' rates and social adjustment scores still persisted at a significant level when this bias was controlled. This indicates that the type of living group to which a patient goes after leaving hospital may have an important bearing on his subsequent career, whatever his residual disabilities are.

Psychiatrists are familiar with the mother who tolerates, and perhaps even encourages, an attitude of child-like dependence in her schizophrenic son: this kind of relationship was especially common in the 53% of unemployed schizophrenics living with their parents, and was very rarely found in other types of living group. Perhaps it is not always beneficial for a schizophrenic to return to the close emotional ties of a parental or marital household.

The relationship of outcome and post-hospital living group was less clear-cut in the patients with other diagnoses, but there was some evidence to suggest that, unlike the

Table 4 - Marital state of "ever-married" schizophrenics and other diagnoses at key discharge by 'success' and 'failure'

	Schizophrenia		Other diagnoses	
	Success	Failure	Success	Failure
Married	7	7	16	1
Widowed, separated, and divorced	16	2	11	14

schizophrenics, they tended to do better in situations involving close personal relationships. For example, *table 4* shows completely contrary results for patients of the two diagnostic groups in respect of their marital state at discharge.

Of the sixteen patients with 'other diagnoses' who 'succeeded' in a marital setting seven were unemployed. In contrast, of the seven schizophrenic patients who 'succeeded' in a similar environment, all but one were employed. These figures suggest that wives found it easier to tolerate a state of dependence in patients of the former group.

In order to reach a just estimate of the outcome of these patients it was necessary to take into account not only their success in avoiding relapse and in attaining a fair level of social adjustment but also the consequences (*social liabilities incurred*) to other persons of the patients' return to living in the community. In some instances, the patient's 'success' was bought at the price of occasioning severe distress to others in his household.

A three-fold rating was, therefore, made of the amount of hardship which the patient's presence imposed on other members of his living group.

17% of the total sample were rated 'severe liability,' 28% 'moderate liability' and 55% 'minimal or no liability.' Many of the patients who caused distress to others relapsed within the year: (79% of those rated 'severe' and 44% of those rated 'moderate liability').

Among the 156 'successes' there were 36 patients (23%) who caused moderate hardship to others, and 8 patients whose presence in the household caused severe hardship. In the case of the latter group it was evident that the burden of a very disturbed patient had only been transferred from the hospital to the home.

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The organization and control of prophylactic trials

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The nature of both the organization and the control depends very much on the disease and on the public health organization in the country where the study is to be made.

The British Medical Research Council pertussis trials for example were locally controlled by locally appointed part-time medical officers and full-time nurse-investigators in a few specially chosen areas.

The British poliomyelitis vaccine study on the other hand required the collaboration of all medical officers of health in the United Kingdom.

The influenza vaccine trials were made in semi-closed communities (groups of soldiers, factory workers, students and nurses).

The B.C.G. trials were made in children about to leave school.

The Yugoslav typhoid vaccine trial required an intensive propaganda effort in a defined community of about 300.000 persons.

Instead therefore of talking about the organization of a particular study I am going to discuss in general terms the need for such studies (for they are expensive and cumbersome and we have to be sure they are required); the principles of procedure; and, finally, their limitations.

Mention of the W.H.O.-Yugoslav typhoid vaccine trial permits me to use the history of typhoid vaccination as an example of the need of such studies being made at an early stage. Typhoid vaccine has been in use since 1896, but until the Osijek trial reported in 1957 (report 1957b) no sound assessment of its value in the field was available, with the result that the literature is an inextricable mixture of science – or rather laboratory studies not necessarily always synonymous with science – and emotion. Yet it now seems after more than 60 years that Almroth Wright had a good antigen after all when he produced his heat-killed phenol-preserved vaccine.

The long delay between the first use of typhoid vaccine and its first test in a properly carried out field trial was not due to lack of a known method of field testing, or of practical suggestions for carrying out the test. Both the method and its practical application were suggested by Karl Pearson in 1904 (Pearson 1904) and again in 1908-09 (Maynard 1908-09) and neither have changed much since.

You may ask where field studies stand in relation to the work of the laboratory. The contribution of the laboratory is of first importance; Marc Daniels (1951), in talking of clinical trials in the chemotherapy of tuberculosis, put the position well, and what he said applies also to field studies of prophylactics. He said: "We should have no illusion concerning the character of this type of clinical research. The major research, the original work, has been done before this ..... stage, in the laboratories of the biochemists and bacteriologists working as individuals or as teams. The methods (of the field study) are simply designed to replace the old method of trial and error which was so costly in time and human lives." In other words, in the field trial a new immunizing agent already shown to have promise in the laboratory is tested for safety and effectiveness in those whom it is desired to protect from illness. It is a direct test. Most laboratory tests are indirect.

The difficulties of field studies lie not in the complexity of the theory behind them but in the practical problems which are encountered in carrying them out. The nub of the problem of a successful field trial is the provision of a satisfactory standard against which the experience of the vaccinated can be measured (for all true measurement is essentially

comparative). The only adequate standard against which the experiences of the vaccinated can be satisfactorily measured is that provided by unvaccinated controls differing from the vaccinated only in one particular – the absence of vaccination. How can such control groups be found in a human population in which the individual persons (or their parents) have a right to accept or refuse to take part? A procedure much used in the past was to ask for volunteers, vaccinate them, and compare the incidence of disease in the volunteers with the incidence in those who did not volunteer. This was the method employed in the very extensive typhoid vaccine trials in the British Army in India from 1904 to 1908 when 1000's of persons were observed. The objection to it is that people who volunteer may differ from those who do not volunteer, and comparisons of attack rates in the two may be fallacious. The point was made by Pearson.

His objection has often been made since, but we have had to wait, I think, for the American trial of poliomyelitis vaccine to find reasonable proof that volunteers do differ from non-volunteers in relevant respects. Clausen and his colleagues (Clausen et al. 1954) studied a group of about 200 mothers, half of whom had volunteered for the poliomyelitis trial and half of whom had not. From the paper it is clear that the mothers who consented to have their children inoculated had attended school longer (and presumably were better educated) and were more likely to discuss the question with the doctor or nurse than those who refused. The consenting mothers also lived under better conditions than those who refused. As social class has a definite influence on the incidence of poliomyelitis at different ages these observed social differences might well have affected the results of the trial.

Less direct but equally interesting observations were made by Rowntree (1950) who studied the diphtheria immunization programme in England and Wales five years after its institution, by which time it was acknowledged as a procedure of established value. She found differences in acceptance rates. First-born children were more likely to be immunized than those born subsequently; some 80% of first-born children were immunized compared with 50% of fourth or later children in a family. Social class also made a difference; 88% of children of the professional and salaried workers were immunized compared with 68% of children of manual workers.

Social class, educational opportunities, and size of family are factors which have to be taken into account in setting up vaccinated and control groups in field studies. There are many others. Sanitation levels would clearly be important in testing vaccines against the bowel diseases; the presence or absence of school children in a family in the testing of common cold vaccines; relatives with tuberculosis in the testing of B.C.G. – not to mention the more obvious factors of age, sex, previous attacks of the disease being studied, previous immunization against it, and so on. The only satisfactory way of obviating the risk of having serious dissimilarities between the vaccinated and control groups, and so far as I can see there are no short cuts to it, is to find sufficient volunteers and divide these volunteers into two (or more) groups by some random method which ensures that no bias enters into the allocation of a particular individual to a particular group. The satisfactory construction of similar groups is the essence of a trial, and if this is not achieved the trial had better not be done.

But other principles have also to be observed. The principles of procedure may perhaps be listed as follows (*a-l*):

a. There must be good presumptive evidence from in vitro, animal, or small-scale human volunteer experiments that the new prophylactic is likely to be of real value.

b. It must have satisfied accepted criteria for absence of toxicity, absence of severe local or general reactions, and absence of untoward sequelae. It must have been administered to increasingly large groups of volunteers without ill effect.

c. The trial must be made only with volunteers (this term includes of course parents who volunteer to have their children inoculated).

d. The aim and method of the study must be explained to the volunteers (or their parents) orally and in writing before they are accepted.

e. As we have said, the volunteers must be divided, by a method which eliminates the risks of bias, into two groups, one to be vaccinated and the other to be kept as a control.

f. Both groups must be observed with the same intensity over the same period.

g. The observers should not know, at the time their observations are being made whether the person they are seeing is in the vaccine or control group.

h. The subjects also should not know to which group they belong until the end of the study.

i. As far as possible an objective method of diagnosis should be used.

j. When observations are to be made by different observers in different areas, a uniform detailed plan must be prepared and adhered to.

k. The trials should be terminated as soon as reasonable statistical evidence is obtained.

l. The results should be analysed and a report prepared with all speed as soon as the trial has ended.

The volunteers must be kept in ignorance of their status – vaccinated or control – so that their interest in the study is maintained. One can imagine that the controls – if they knew they were controls – might loose interest before the vaccinated.

The observers should not know the status of a participant. Otherwise they will find it difficult to make a confident assessment of a doubtful case. This means then that the volunteers in the control group should seem to be given exactly the same treatment as the vaccinated: injections with an inoculum of the same appearance as the vaccine if the vaccine is injected, capsules if the vaccine is given by mouth. The vaccine and the placebo (to use the American term for the control material) must therefore appear the same and be identifiable only by some coding system.

Different methods have been used in the allocation of children to the vaccinated and control groups. In most trials use has been made of random sampling numbers for allocation of the children. This was employed in the early British pertussis vaccine trials (Report 1951, 1956), the influenza vaccine trials (Report 1953, 1957, 1958), the B.C.G. trials (Report 1956b), and in the Yugoslav typhoid vaccine trials (Report 1957b). In the American poliomyelitis vaccine trial (Francis et al. 1955) the vials of vaccine were issued in containers each of which had an equal number of vaccine and control vials. In the later British pertussis vaccine studies (Report 1956) children were allocated in accordance with the date of birth – children born on odd days being given one vaccine, and children born on even days another – a very simple procedure which I can commend, provided of course it is remembered that more children are born on odd days of the year than on even days. In the British poliomyelitis vaccine study (Report 1957c) the month of birth was used. I have said that the control group must be given precisely the same treatment – injection or whatever – as the vaccinated. But this is not always possible. In the B.C.G. studies in the United Kingdom it was impossible to try and simulate the local lesion, and the controls were given nothing. It was thought that prior to the administration of the B.C.G. both controls and vaccinated had had so many Mantoux tests and X-rays that they would be sufficiently confused not to know whether they were vaccinated or not. I do not know if this was a justifiable supposition, but as an objective diagnostic criterion (the X-ray) was available, I doubt if bias crept in. Similarly in the British poliomyelitis vaccine trial controls were not inoculated because of the immense numbers of children in

the study. Again, as all paralytic cases of poliomyelitis are admitted to hospital, and as paralysis is a reasonably objective sign, the fear of bias could probably be discounted.

It used to be said that it would be impossible to obtain volunteers for such studies in which half the children were not given the test vaccine. But experience has shown this to be entirely wrong. In the early pertussis trials 9.000 parents brought their children into the scheme; in the B.C.G. studies there were 57.000 volunteers; in the Yugoslav typhoid vaccine trial 39.000, and in the controlled part of the American poliomyelitis trial 450.000. It is clear therefore that in many parts of the world volunteers for scientific field studies of this kind are not slow in coming forward. Not only because they have a chance of immediate gain, but also because they are interested in contributing to medical science. Of the mothers interviewed in Clausen's study (Clausen et al. 1954) 24 per cent said the main reason for entering their children's names for poliomyelitis vaccination was because it would contribute to medical research. It is clear therefore that here is a practical method for the evaluation of new vaccines. Few would now deny that it is an essential prerequisite for the acceptance of all new antigens. But as I have already said the trials are clumsy, they require immense numbers of persons if the incidence of the disease is low, they depend often on observations by many different observers working under different conditions and, in the end, they give approximate and not precise information.

The field trial therefore has to be looked on as only a part of the investigation. Extensive concomitant laboratory studies have to be made in an effort to devise and restart reliable laboratory methods to measure the capacity of the antigen to protect those inoculated with it. There is no time to develop here the question of the relation between laboratory tests on the one hand and protection of human beings on the other. Sufficient to say that where the disease is not reproducible in small laboratory animals the results of laboratory estimates of potency must always be taken with reservations. In such diseases comparisons between performance in the field and assays in the laboratory should be made on as many different batches of vaccine as possible, in order to gain the maximum information on the relations between the field and the laboratory.

Field trials of new prophylactics in the past 15 years have added greatly to the sum of knowledge on the value of active immunization, and no doubt they will continue to do so, but let us not forget that the next great step required is to be made in the laboratory: the elucidation of the mechanism of immunity and of methods to measure it confidently. When that has been achieved the field study will have served its purpose, to be replaced perhaps by a few tests of a few batches of vaccine on a small number of susceptible volunteers.

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Epidemiology of enteroviral infections

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The groups of poliomyelitis, Coxsackie and ECHO viruses possess the property of propagating in the human alimentary tract and of being excreted in the pharyngeal secretions and the stools.

All three groups of viruses may produce the syndromes of febrile pharyngeal or gastrointestinal illness, aseptic meningitis and, occasionally, encephalitis. The most characteristic clinical feature of infection with the poliomyelitis viruses is the paralytic attack. There is, however, accumulating evidence that certain types of the Coxsackie and ECHO group of viruses may also produce, usually mild, paralytic attacks.

Besides the syndromes mentioned, group A Coxsackie viruses may be etiologically associated with herpangina, and group B Coxsackie viruses may produce pleurodynia, epidemic myalgia or Bornholm disease. Moreover, group B Coxsackie viruses have recently been demonstrated as a cause of infantile myocarditis. After all, myocarditis may also be etiologically associated with poliomyelitis.

Since this laboratory has been engaged in the diagnosis and research of enteric virus infections for several years, it has been shown that the 3 groups of enteroviruses are widely disseminated among the population of the Netherlands. A consequence of the existence of various groups and types of enteroviruses is a break-down of the epidemiology of enteroviral infections in the epidemiology of diseases caused by the various types in each of the groups of enteroviruses. On one hand, a wide variety of enteroviruses may produce a given clinical syndrome, e.g. aseptic meningitis, and on the other hand, a given type of virus may produce a variety of clinical syndromes varying from minor illness to encephalitis or paralytic disease simulating poliomyelitis.

Poliomyelitis

Since poliomyelitis is a notifiable disease, three patterns of reported annual incidence are noticeable:

1. low incidence (less than 5 per 100.000), characterized by sporadic cases,
2. moderate incidence (5 to 10 per 100.000), characterized by one or more epidemic foci,
3. high incidence (more than 10 per 100.000), characterized by either extensive epidemic foci or by a generally increased incidence.

Years of increased incidence, either moderate or high, occur every 4 to 5 years (*fig. 1*), with the exception of the period between 1930 and 1938, when a constantly low incidence has been reported. Almost all of the epidemic years are preceded by a year with relatively increased incidence, which could be referred to as a pre-epidemic year.

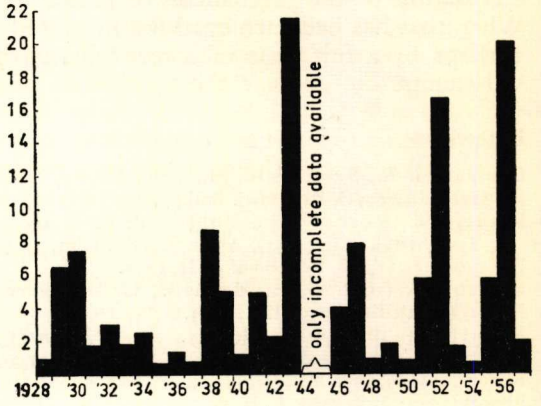

Fig. 1. Poliomyelitis morbidity per 100.000.

Aided by grants from the National Health Research Council T.N.O., the Princess Beatrix Polio Foundation and the State Institute for Public Health.

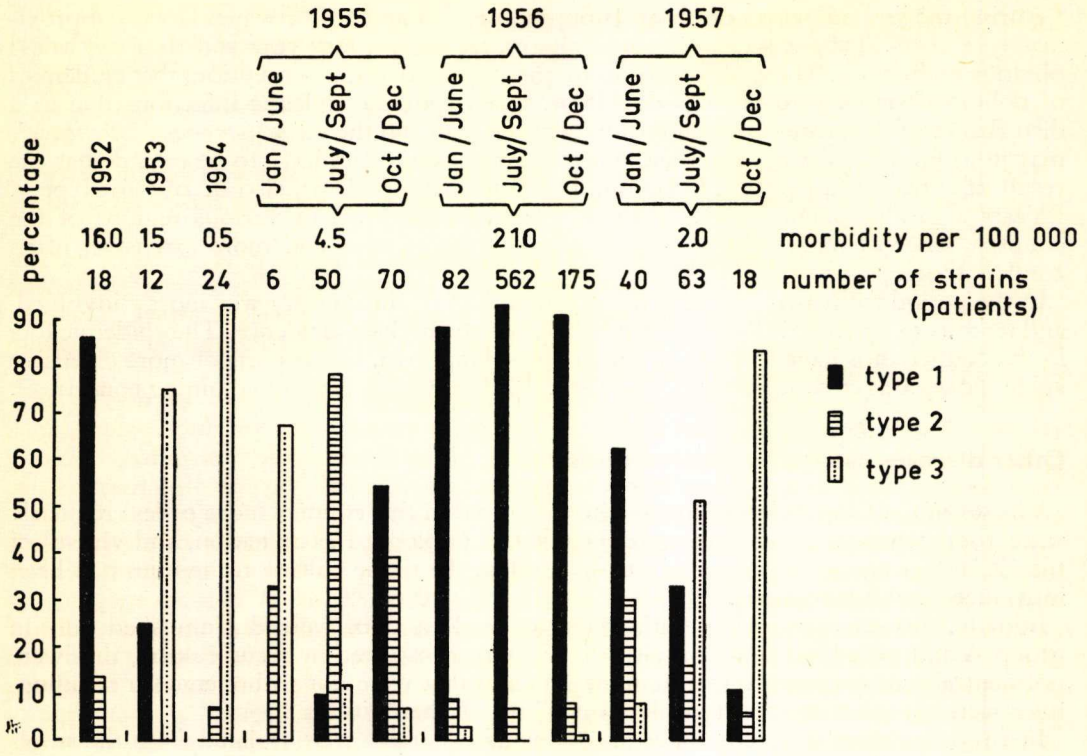

Fig. 2. Fluctuation in the prevalence of poliomyelitis viruses

A regular virological examination and typing of isolated strains have been performed since 1949, initially by inoculation of monkeys [5] and since 1952 by the tissue culture method, first with the use of HeLa cells, and since 1955 with the use of monkey kidney cells.

Although before 1952 the number of strains isolated and typed is too small for being included in *fig. 2*, and the period under observation is limited, the fluctuation in the prevalence of the 3 types of poliomyelitis virus is clearly illustrated. Years with a high incidence (1952 and 1956) are characterized by a predominance of type 1 (approximately 90 per cent of the isolated strains). The type 1 periods are followed by type 3 periods, and the type 3 period of 1954 is followed by a type 2 period. At this time, it is not yet known whether the type 3 period of 1957 will also be followed by a type 2 period. Both type 2 and type 3 periods are characterized by a low incidence.

When looking at the type 1 period of 1956, it is obvious that the relative incidence of type 1 was already increasing during the last 3 months of 1955 [1], reached its peak in the summer of 1956 and decreased rapidly during 1957. A similar wave shows the relative incidence of type 3.

When the relative incidence of a given type decreases, that of another type is increasing. Hence, the incidence of two types may be in a relative equilibrium for a short period, e.g. type 2 and type 1 at the change-over from the third into the fourth quarter of 1955, and type 1 and type 3 in the middle of 1957.

During the limited period of observation, both type 1 and type 3 waves last for approximately 2 years. Type 2 seems to occur almost regularly every year and to show a less obvious undulation. These observations might indicate that the conception, that epidemics of poliomyelitis have to be regarded as increased sporadic-endemic infections due to a disturbance of the symbiotic equilibrium between man and the virus (*commensal infections*) [4], may fit as far as type 2 is concerned, but that type 1 epidemics have to be regarded as the result of spread of a parasitic infection. The latter may, perhaps, also be true for type 3.

Years with a moderate incidence show a few epidemic foci in various regions of the country, whereas those with a high incidence show several and more extensive, often confluent foci.

In the period from 1930 to 1947, the northern half of the country was mostly involved, and from 1952 up to now the southern half shows the highest incidence. The epidemic foci in the Netherlands have to be regarded not as solitary foci, but as parts of more extensive epidemic regions covering parts of the Netherlands as well as parts of adjoining countries [3].

Other diseases caused by enteroviruses

Viruses of the Coxsackie group have been isolated in this country more or less regularly since 1951, when suckling-mice were included in virological examination, and viruses of the ECHO group were isolated since 1952, when the tissue culture techniques had been introduced in this laboratory.

Initially, viruses that proved pathogenic for sucklingmice were distinguished only in group A and group B Coxsackie viruses, and viruses isolated in tissue culture, that were not neutralized by poliomyelitis immune sera and that were not pathogenic for suckling-mice were regarded as "non-typable viruses" or "orphan viruses".

In 1955, a relatively large number of Coxsackie B_4 strains were isolated from the stools of patients suffering from febrile pharyngeal or gastrointestinal illness, pleurodynia, aseptic meningitis and encephalitis, and from the myocardium of newborn infants who died from myocarditis or encephalomyocarditis [6]. In 1956, an extensive outbreak of $ECHO_9$ virus disease occurred simultaneously with an epidemic of poliomyelitis.

The short period in which regular typing of Coxsackie and ECHO viruses has been performed does not allow any conclusion as to a fluctuation in the prevalence of certain relatively high pathogenic types of these viruses. It seems, however, that certain strains of the Coxsackie B group and $ECHO_9$ virus are highly prevalent during a period of 1 to 2 years, and then almost or entirely disappear for an unknown period.

Poliomyelitis and $ECHO_9$ virus disease in 1956

The number of notified cases of poliomyelitis from 1955 through 1957 is recorded in *fig. 3* (information given by the Chief Medical Inspector of Public Health). The peak in the epidemic year 1956 was reached in August, i.e. 2 months earlier than in the pre-epidemic year 1955 and one month later than in the post-epidemic year 1957.

The percentage of reported non-paralytic cases in 1956 is relatively high. Since the simultaneously occurring outbreak of $ECHO_9$ virus disease yielded a considerable number of cases of aseptic meningitis, many of those have presumably been reported as non-paralytic poliomyelitis.

Since aseptic meningitis is not a notifiable disease, the number of cases is unknown. It can be concluded, however, from the large number of $ECHO_9$ strains that have been isolated that this epidemic was spread all over the country. The simultaneous occurrence

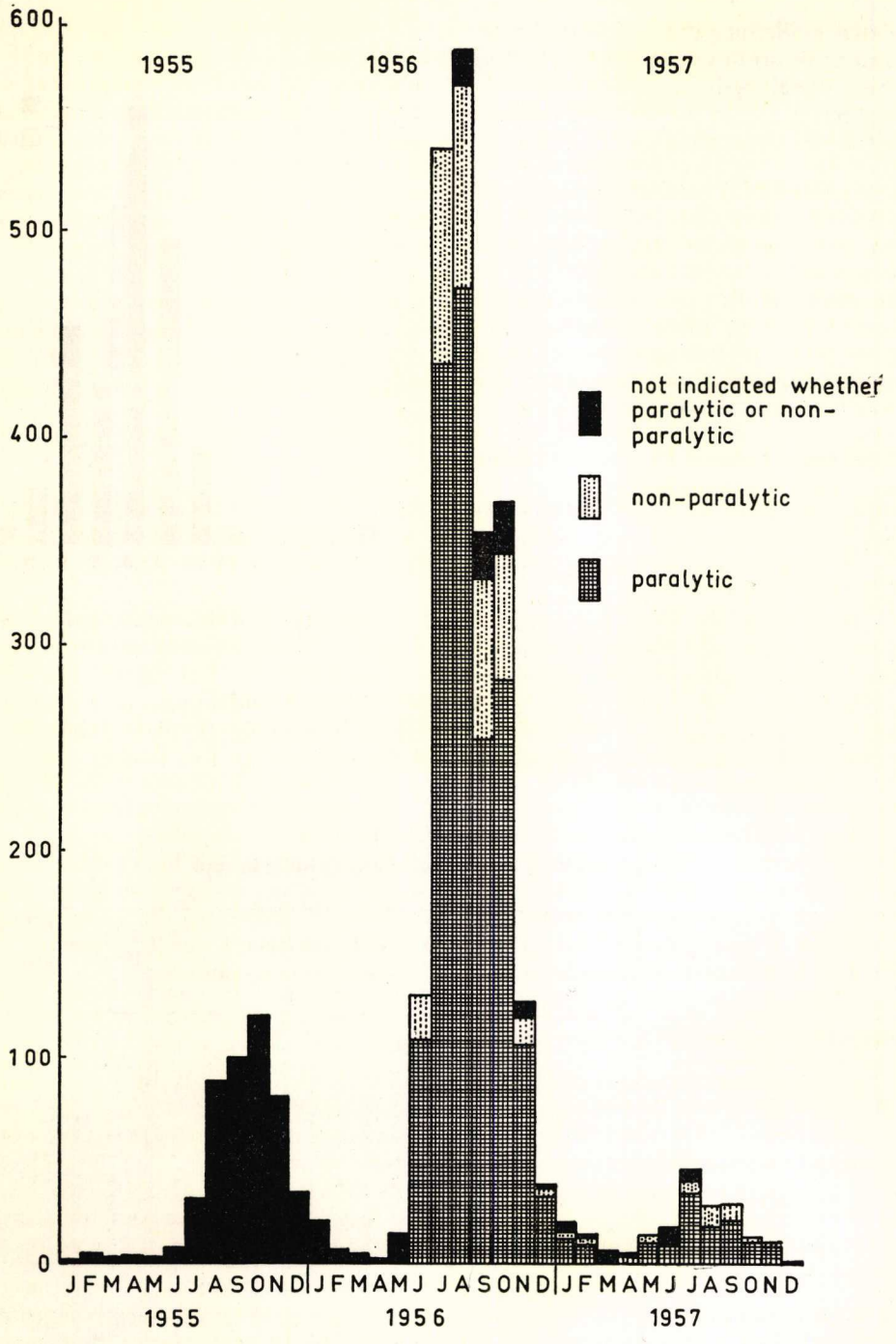

Fig. 3. Number of notified cases of poliomyelitis

of the two epidemics can be inferred from the number of strains isolated (*fig. 4*). Both epidemics developed in June and July, reached their peaks in August and declined during the next months.

The dominating types were type 1 of the poliomyelitis group (91 per cent of 718 strains), type A_5 of the Coxsackie group (52 per cent of 77 strains) and type 9 of the ECHO group (98 per cent of 527 strains) (*table 1*). At least 15 different types of virus belonging to 3 different groups of enteroviruses were isolated from patients suffering from various clinical syndromes, which all may be due to infection by each of the 3 groups of viruses. Moreover, mixed infections were not uncommon.

The enteroviruses were found to be excreted by patients for a considerable period of time (*fig. 5*). In all forms of poliomyelitis, the virus was found to be excreted for at least 4 weeks in a relatively high percentage of the patients. In paralytic poliomyelitis the percentage of virus excretors decreased rather slowly from the first through the fifth week of illness, and in two patients the virus was found to be excreted for at least 39 and 67 days respectively. Similarly, the Coxsackie and ECHO viruses were found to be excreted for periods up to 4 weeks.

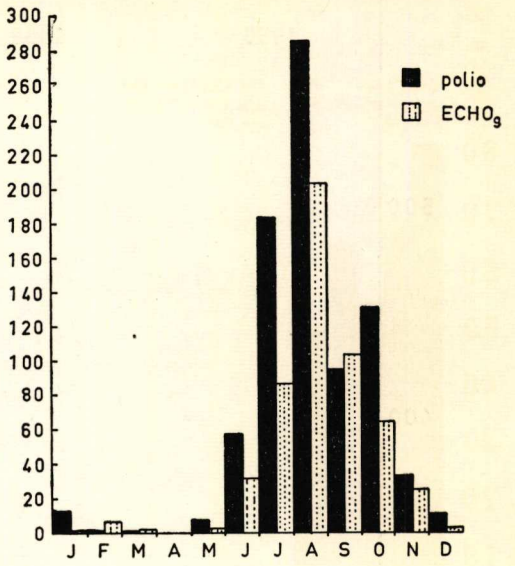

Fig. 4. Number of poliomyelitis virus and $ECHO_9$ strains isolated in 1956

Table 1 - Type distribution of enteroviruses in 1956

Month	Poliomyelitis virus types			Group A Coxsackie virus types									Coxs. B type 1	Echo group	
	1	2	3	2	3	4	5	6	7	10	16	19		type 9	other types
Jan.	12	2	–	–	–	1	–	–	–	–	–	–	–	1	–
Febr.	1	–	1	1	–	–	–	–	–	–	–	–	–	6	–
March	1	1	–	–	–	–	–	–	–	–	–	–	–	3	–
April	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
May	7	–	–	–	–	–	–	–	–	–	–	–	–	2	–
June	51	4	2	1	–	1	5	–	–	1	–	–	–	31	–
July	169	10	4	3	1	–	20	1	2	2	–	–	3	85	1
Aug.	264	21	–	4	–	2	10	–	–	6	2	–	4	195	8
Sept.	86	7	1	1	–	2	4	–	–	–	–	–	1	102	1
Oct.	121	8	1	–	–	2	–	–	–	1	–	2	–	64	–
Nov.	27	5	1	–	–	–	1	–	–	–	–	1	1	25	–
Dec.	10	1	–	–	–	–	–	–	–	–	–	–	–	2	1
1956	749	59	10	10	1	8	40	1	2	10	2	3	9	516	11
Percent. per group	91	8	1	13	1	10	52	1	3	13	3	4		98	2

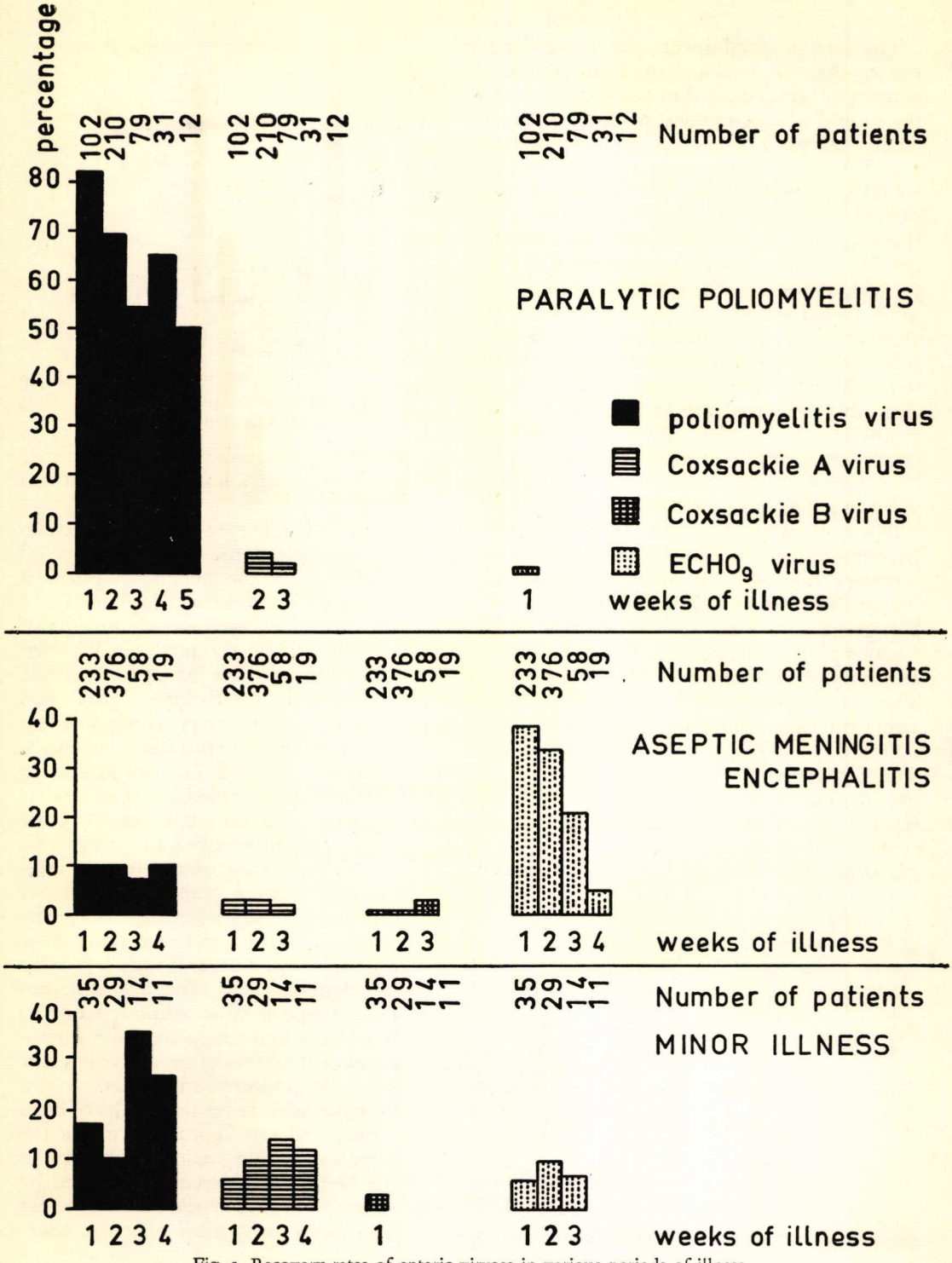

Fig. 5. Recovery rates of enteric viruses in various periods of illness

The data obtained during the 1956 epidemics show, that the seasonal distribution and the pattern of virus excretion are common epidemiological characteristics of the 3 groups of enteroviruses. The age distribution, however, is different, at least as far as poliomyelitis and $ECHO_9$ virus infection are concerned. *Fig. 6* shows a marked peak of poliovirus isolations in the 1 to 5 year age group and a sharp decline towards the lower and the higher age groups. Although the percentage of $ECHO_9$ virus isolations is also highest in the 1 to 5 year age group, the peak is less marked than that of the poliovirus isolations and the decline towards older age groups is much slower. This indicates that the immune status of the population against $ECHO_9$ virus infection is much lower than that against poliovirus infection which is presumably a reflection either of a recent introduction of $ECHO_9$ virus in this country, or of a limited spread of this virus in preceding years.

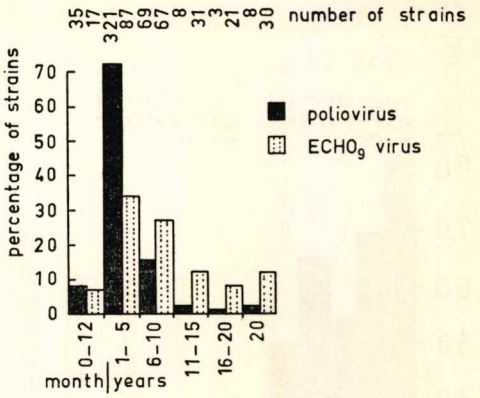

Fig. 6 Age distribution of poliomyelitis and $ECHO_9$ strains isolated 1955-1757

The immune status of the population against poliomyelitis is reflected by the parallelism between the age distribution of the reported cases of poliomyelitis, the poliomyelitis viral recovery rate and the antibody triple negative individuals in the general population (*fig. 7*). The poliomyelitis antibody pattern in approximately 2000 normal individuals of all age groups, the majority of them originating from lower socio-economic groups of various parts of the country [2], shows a picture similar to that of other countries in Western Europe (*fig. 8*). The percentage of sera possessing antibody to any type increases with age. The occurrence of the recent major outbreaks of poliomyelitis due to type 1 (1956 and 1952) and those which have presumably been due to type 1 (1947 and 1943) is more or less reflected in the pattern presented. This pattern shows to a certain extent 4 different levels. The highest level (80 to 90 per cent of the sera possess type 1 antibody) occurs in the age groups older than 13. These individuals have been through all 4 epidemics. The second level is that of the 10 to 12 year age group, which has been through 3 epidemics (75 per cent of the sera positive), the individuals of the third level (age group 4 to 9; 50 to 60 per cent positive sera) have been through 2 epidemics, and those of the fourth level (6 months to 3 years; 20 to 40 per cent positive sera) through only one epidemic. Type 2 and 3 antibody show a gradual increase and such levels are not demonstrable. The age distribution of type-specific antibody seems to be in close agreement with the fluctuation in the prevalence of the different types of poliomyelitis virus. It can be concluded from the results of both typing and serological survey of the population, that major epidemics in the Netherlands have been caused by type 1, and that types 2 and 3 so far have been responsible only for scatt-

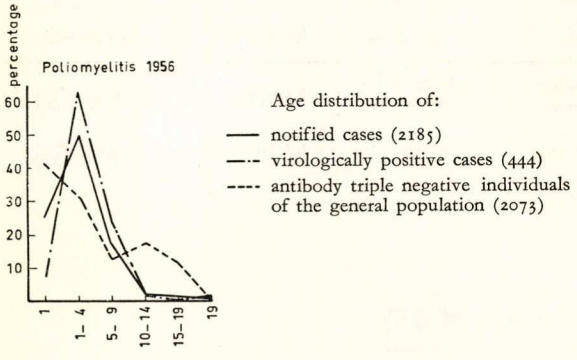

Fig. 7. Age distribution of 2185 notified cases of poliomyelitis

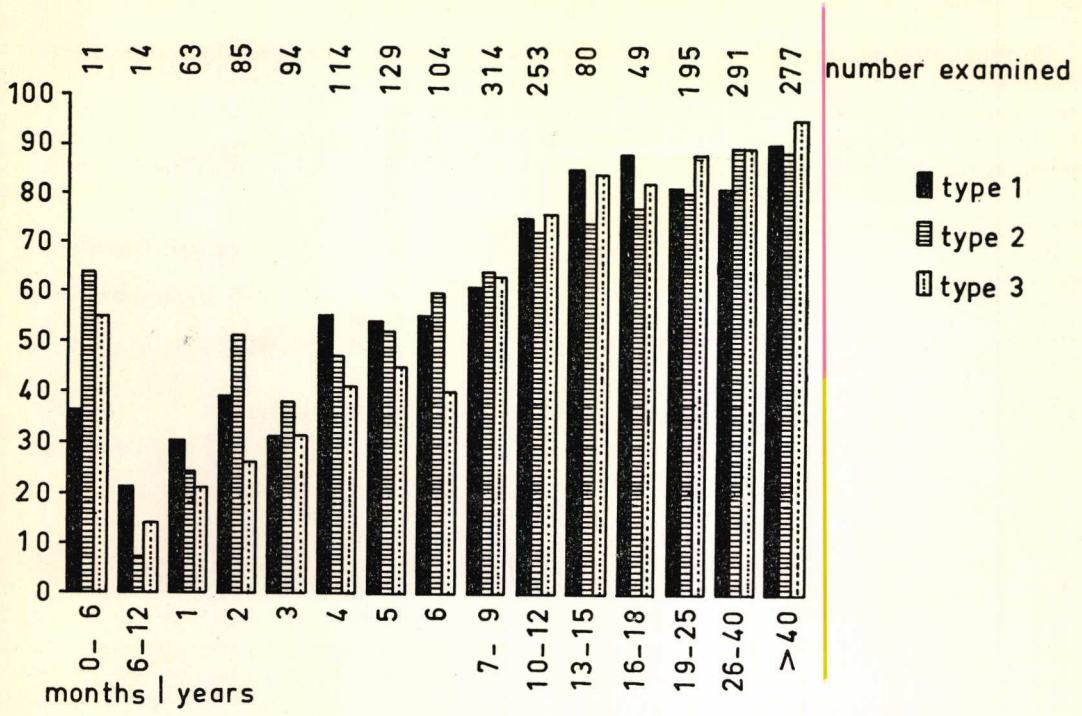

Fig. 8. Age distribution of poliomyelitis neutralizing antibody in 2073 individuals from the general population.

ered cases or limited outbreaks of paralytic poliomyelitis. The gradual increase of the percentages of type 2 and type 3 antibody-possessing sera, however, indicates that these types are spread as widely as type 1. The four levels of type 1 antibody in the general population might indicate that this type of virus is dominating only in epidemic years, whereas at least type 2 is widely spread every year. Type 3 might take an intermediate position.

Conclusions

During the last 20 years, a relatively high incidence of paralytic poliomyelitis has been observed every 4 to 5 years. Virological examination has shown, that such years are characterized by a predominance of type 1, whereas the interjacent periods with a relatively low incidence are characterized by a predominance of either type 2 or type 3. Type 2 seems to occur every year. Type 3, however, shows some fluctuation in its prevalence more or less similar to that of type 1. The age distribution of type-specific antibody as derived from an antibody survey of the population shows 4 levels of type 1 antibody, reflecting the number of epidemics through which various age groups have gone. Such levels of type 2 and type 3 antibody were not demonstrable, but the gradual increase of these antibodies with age up to approximately the same level as type 1 antibody, indicates that all types are equally distributed. Type 1, however, dominating in epidemic years only.

Outbreaks of other enteroviral infections have been studied for a few years only. In 1955 Coxsackie B_4 infections and in 1956 $ECHO_9$ infections were prevalent, both being etiologically associated with various syndromes, a.o. aseptic meningitis.

During simultaneously occurring outbreaks of poliomyelitis and $ECHO_9$ virus disease, the seasonal distribution and the pattern of virus excretion were found to be common epidemiological characteristics. The age distribution however, was different, since 80 per cent of the strains of poliovirus was isolated from individuals of the 0 to 5 year age group, whereas only 40 per cent of the $ECHO_9$ strains isolated originated from this age group.

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A project for rural medical care

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Dr. Dean Fisher, the commissioner of health for Maine, the northernmost state of the eastern seaboard, has long had an interest in providing the best possible care for the elderly, and for patients with chronic disease and static handicaps. However, the State of Maine cannot afford expensive facilities, and it is his feeling that an effective system of comprehensive care can be developed by the alternative method of close co-operation between practicing physicians, hospitals, and health department.

Several years ago, Dr. Wilson Smillie did a survey of the health needs of Maine and confirmed that better care must be made available for the aged, for mental illness, for patients with handicaps, and for patients with degenerative diseases. He found that the present percentage of people in Maine over the age of 60 equals the expected percentage for the country as a whole in 1990. Therefore, any plan which might be proven successful in Maine would serve as a prototype for the rest of the country to meet this future need.

The Bingham Associates Fund has for many years been interested in improving rural health, and most of their activities have been devoted to Maine. Dr. Jean Curran, medical consultant to the Bingham Associates Fund participated in the survey with Dr. Smillie, and was convinced that a scheme for comprehensive care should be tried.

It was decided to locate the project in Waterville, Maine, because through the years two people had worked together to create an environ particularly suited for the experiment. Dr. Frederick Hill had returned to his native Waterville after medical training in Boston, and, being unsatisfied with the available hospital services, had started a hospital of his own in a private home. Miss Pearl Fisher, a nurse with a particular talent for administration, became director of the hospital. Through their efforts, the Thayer Hospital has grown to its present status, a modern 97-bed hospital on the Mayflower Hill campus of Colby College. One wing of 37 beds is devoted to the care of the chronically ill and the handicapped. The medical care provided in the hospital is of the highest standard. A director of Medical education, Dr. George Robinson, was added to the staff, and a careful weekly review of the medical care of all admissions was instituted. Thus Waterville provided a setting of excellent medical care for patients admitted to hospital. However, the community facilities available to practitioners for their patients who did not require hospitalization were almost totally lacking. Basic public health procedures were directed by a layman, and there was no appropriation for visiting nurse service, or other services that would bridge the gap between hospital and home.

Waterville has two other hospitals besides the Thayer Hospital. Close liaison has been developed with one of them – the Catholic Hospital. The other is an osteopathic hospital and it has not been included in the planning.

I have recently been appointed as director of the project and am very pleased to have this opportunity of discussing it with an international group of epidemiologists. I do not start in Waterville until the first of August, but have some questions already formulated that I would like your advice on.

The first question is to decide whether the project should be done as a service project, as a demonstration, or as a research project. I believe that it will probably turn out to be somewhat of a combination.

Let us assume that it will be evident after some study that there is particular need for a visiting nurse service, a rehabilitation center, and a home care program. Let us further assume that these services are set up and are accepted by the community. What sort of

evidence would this group want at the end of the project to prove that adding these services was worthwhile? Would they want:

a. A survey at the beginning and end of the project comparing the disability rates?

b. Would they prefer that services were given to alternate patients, so that a controlled series could be presented?

c. Should attempts be made to compare the cost of disability to the community before and after the services had been set up?

d. Should another comparable community be studied along with Waterville, and comparisons made before and after?

e. Finally, should the approach be the same as setting up a department in a medical school - keeping careful records of plans and what had been completed in a certain period of time without attempts to justify the plans in terms of statistics?

I look forward to hearing some discussion on these points. I am particularly anxious also to hear how one of our Dutch colleagues is at present approaching a similar problem.

Family health study in The Netherlands

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The World Health Organization has been interested in local health service because it is a health measure directly concerning the attainment of the highest possible level of health of all people of the world
A Report of the Study Group on Local Health Service, 13-17 December 1954, Geneva.

A few years ago WHO initiated a programme of local health study in order to get a better picture of the possibilities and also the shortcomings of local health services in various parts of the world. On the basis of an „Outline of Local Health Study" three European countries undertook pilot studies.

The present study is performed in the Department of Public Health of the University of Leyden, of which Prof. Dr. P. Muntendam is the director. It is part of this WHO study programme and it is being carried out in the town of Zutphen. Subsidized by the National Health Research Council of The Netherlands it also received a grant from the World Health Organization.

The main object of the study is to investigate the relationship or importance of various environmental, social, economic and health factors affecting the pattern of family living. The health status of individual families is followed closely during a whole year in relation to what the family has received in the way of health services and how the family is participating in the socio-economic life in conjunction with any important changes in its environment. Zutphen has a population of 25.000, of which a random sample of 550 families has been taken for the purpose of this study. The collection of data is being performed by way of the interview method.

Apart from questions asked directly in connection with the health status of individual family members and the utilization of health facilities, questions are also put concerning diet and housing conditions. To record these data three separate questionnaires were designed. The dietary survey is performed by a dietician and the housing survey by two housing inspectors, both visiting all families at two separate occasions. For the medical survey 5 visits per family are made at three-monthly intervals. Interviewers are one public health nurse and one physician, in charge of the Zutphen study.

In the near future the interview period will be completed and the tabulation and statistical analysis of the data will be started.

CONTENTS