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The Hazards of Immunization

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PREFACE

IT MUST SELDOM occur that a subject in which from time to time there has been widespread interest finds itself still without an expository volume. And yet that is how it stands with the subject about which I am writing. Though there are a few excellent descriptions of individual portions of the subject, and several brief accounts of other portions, to the best of my knowledge no book has yet appeared that essays to present a conspectus of them all. Popular or more serious authors must have considered undertaking such a task and for one reason or another decided against it; and it is therefore with more than usual diffidence that I venture to offer the present review of the subject to the scientific public.

That the book will be criticized on the ground that the digging up of so many unsavoury facts is neither necessary nor expedient, and that it will merely strengthen the case of the anti-vaccinationists, I am well aware; but what has influenced me most in its preparation is the need to understand how mishaps have arisen, so that with the exercise of due care they may be avoided in the future.

It is clear that, so far as *accidents* are concerned, most have occurred in association with a new prophylactic agent made by a reputable well-established laboratory or with some normal product made by a small, often local, laboratory dependent on the services of technicians devoid of the necessary skill and experience and ignorant of the many pitfalls in their path. A thorough understanding of the cause of their failure cannot but serve as a useful warning to others.

The *complications* of immunization present a more difficult problem. It is true that the cause of some of them, especially those due to microbial contamination, can be adequately accounted for; but there are others, such as those associated with the abnormal reactivity of the immunized subject, for which we have as yet no satisfactory explanation. Our aim, therefore, must be to study these as fully as possible in the confident expectation that, as in other branches of science, knowledge will bring enlightenment.

In the Introduction I have described briefly how this book came to be written. Here I can only thank those who have helped me during its compilation, and apologize for its many deficiencies. The subject is one that demands a far more thorough treatment than I have been able to give it. But I put it forward in its present rather elementary form in the hope that it will stimulate someone more versed in the historical method than myself to produce a worthier volume.

Apart from Dr E. T. Conybeare who was kind enough to read through Chapter 15 and put his extensive store of information on post-vaccinal encephalitis at my disposal; Dr A. T. Roden, also of the Ministry of Health, who allowed me to make extracts from some documents of special interest; and the late Dr J. R. Hutchinson who, when he retired from the Ministry, handed over to me a copy of records he had kept during the war years of various accidents that had occurred in the civil and military population—my thanks are due mainly to the numerous librarians and their staffs who have enabled me to consult long-neglected volumes buried in the basement containing the original description of some immunological disaster or other.

Collection of the information I sought has not been easy. Whenever possible, I have been to the original source, but when no original source existed because no account of the incident was ever published, I have not

hesitated to make use of private documents so long as they were fully authenticated.

I should particularly like to express my thanks to Mr V. J. Glanville and his devoted staff of the library of the London School of Hygiene and Tropical Medicine for the unstinted help they have given me; to Mr F. M. Sutherland of the library of the British Medical Association for kindly allowing me access to some of the older volumes of journals that were unobtainable elsewhere; to Miss Betty Whyte of the library at Colindale for her assistance in tracking down a few of the more obscure references; and to the librarian of the Royal College of Surgeons, Mr W. R. Le Fanu, for many useful discussions.

In the preparation of the Heath Clark lectures themselves on which this book is based, I have to thank the Dean, Dr E. T. C. Spooner, and his secretary, Miss Ann Bates, for their continual help in many different ways; Dr Jonas Salk, Dr Hilary Koprowski and Dr Albert Sabin for providing me with photographs of themselves of special interest to the audience; Mr C. J. Webb for preparing so many excellent lantern slides; and Brigadier Sir John Boyd for his kindness in taking the chair at the first lecture. I must also thank the School Council of the London School of Hygiene and Tropical Medicine and the Senate of the University of London for inviting me to give the lectures and for permitting the publication of this expanded version.

Finally I cannot express too strongly my gratitude to Dr R. A. O'Brien who, long after his retirement from the directorship of the Wellcome Physiological Research Laboratories at Beckenham, handed over to me a valuable set of documents with which he felt unable to cope and without which it is doubtful whether the present book would ever have been written.

London, 1966 G.S.W.

CONTENTS

1. INTRODUCTION: PURPOSE AND TERMINOLOGY
2. CLASSIFICATION OF ACCIDENTS AND COMPLICATIONS
3. NORMAL TOXICITY: SIMPLE REACTIONS TO BACTERIAL VACCINES
4. FAULTY PRODUCTION: INHERENT TOXICITY OR INFECTIVITY
5. FAULTY PRODUCTION: FOREIGN TOXIN PRESENT
6. FAULTY PRODUCTION: USE OF WRONG CULTURE
7. FAULTY PRODUCTION: BACTERIAL CONTAMINATION OF VACCINE OR ANTISERUM
8. FAULTY PRODUCTION: VIRAL CONTAMINATION OF VACCINE OR ANTISERUM
9. FAULTY ADMINISTRATION: USE OF NON-STERILE APPARATUS
10. FAULTY ADMINISTRATION: CONTAMINATION FROM OPERATOR
11. ALLERGIC MANIFESTATIONS: LOCAL ALLERGY
12. ALLERGIC MANIFESTATIONS: SERUM SICKNESS
13. ALLERGIC MANIFESTATIONS: SERUM NEURITIS
14. ALLERGIC MANIFESTATIONS: POST-VACCINAL NEURITIS
15. ALLERGIC MANIFESTATIONS: ENCEPHALOMYELITIS AFTER SMALLPOX VACCINE
16. ALLERGIC MANIFESTATIONS: COMPLICATIONS, INCLUDING NEUROPARALYSIS, AFTER RABIES VACCINE
17. ALLERGIC MANIFESTATIONS: ENCEPHALOMYELITIS AFTER OTHER VACCINES
18. ALLERGIC MANIFESTATIONS: SERUM ECEPHALOMYELITIS
19. GENERAL ANAPHYLAXIS AFTER ANTISERA
20. GENERAL ANAPHYLAXIS AFTER VACCINES
21. ABNORMAL SENSITIVITY OF PATIENT: SKIN COMPLICATIONS OF SMALLPOX VACCINATION
22. ABNORMAL SENSITIVITY OF PATIENT: LOCAL OR GENERALIZED TUBERCULOSIS AFTER BCG OR VOLE BACILLUS VACCINES OR TUBERCULIN
23. ABNORMAL SENSITIVITY OF PATIENT: COMPLEX REACTIONS AFTER OTHER VACCINES
24. INDIRECT EFFECTS: DAMAGE TO THE FOETUS
25. INDIRECT EFFECTS: PROVOCATION DISEASE
26. CONCLUSIONS

REFERENCES: Note from Soil and Health Library: The reference section was so entirely daunting to scan/ocr that, despite the size of the download this lazy practice requires, it has been provided as a separate download in the form of bitmap images that are not searchable. It is assumed that very few readers will follow up the references.

I

INTRODUCTION: PURPOSE AND TERMINOLOGY

IN FEBRUARY 1929 the Trustees of the late Mr C. Heath Clark gave the University of London a sum of money to found a Lectureship in the History and Progress of Preventive Medicine and Tropical Hygiene. Under the terms of the Trust Deed as amended in 1930 and 1936 the general scope of the lectures to be given is defined as including the educational, cultural and humanistic aspects—as opposed to technical and manipulative training—of the history development and progress of Preventive Medicine and Tropical Hygiene and their sanitary and social evolution in both temperate and tropical climates. The lectures are given annually, usually in the autumn, at the London School of Hygiene and Tropical Medicine.

The University very kindly offered me the lectureship for 1966. I readily accepted the invitation; and the present book is based on the series of four lectures I delivered in November of that year.

These lectures afford an opportunity for reviewing subjects on a wider basis than most individual workers would do for themselves; and for trying by a careful weighing of the evidence, both observational and experimental, to arrive at generalizations which it should be the aim of all scientific workers to reach, and at an assessment of the value of various procedures that have contributed to a given end.

The choice of subject was one that I had had in mind for a long time. In 1959 Dr R. A. O'Brien, who for many years before the second world war had been director of the Wellcome Physiological Research Laboratories at Beckenham, wrote to me from Australia, where he had retired, offering me a mass of records that he had collected on various disasters associated with immunization.

Though many of them had been published—in different languages in different countries and at different times—some had not; and it occurred to me that it might be of historical value to go through them and collect them together into a single volume. While I was director of the Public Health Laboratory Service, I had no time for this, but after I retired in 1963 I took up the project and began to work on it. Consequently when I received the invitation from the University to deliver the Heath Clark lectures, I realized that they would afford an admirable opportunity to develop my theme.

PURPOSE OF THE PRESENT SURVEY

There is no need here for me to enter into the history of immunization against infectious disease (see Parish 1965). Though in one rudimentary form or another protection against disease by biological means may have been employed for many centuries, and though Edward Jenner may not have been the first to vaccinate against smallpox, it was Jenner's work that formed the real basis of our modern immunological procedure.

The practice of vaccination was carried out for about a hundred years before its theory was understood, and before the nature and causation of its attendant risks began to be appreciated. During this time strong opposition developed towards vaccination, and a campaign of slander and wilful misrepresentation was vigorously pursued by a small but influential group

of the populace. It is still carried on, though less vigorously, by those who are influenced more by emotion than by reason; but of recent years opposition to mass vaccination has sprung up from a quite different source, namely from scientific workers moved not by emotion but by factual evidence.

In any truly democratic country opposition and the freedom to express opinions contrary to those of the majority are the breath of life, and it is thoroughly wholesome for long-adopted practices to be submitted from time to time to critical scrutiny lest the accumulated weight of precedent is allowed to obscure the need for their discontinuance.

My purpose in these lectures is not to battle or to join sides with the anti-vaccinationists, or to take up any partisan attitude, but to try soberly and honestly to present such information as we have on the hazards attending vaccination against smallpox and immunization against other diseases.

Terminology

Here I may perhaps be allowed to digress for a moment to refer to the subject of terminology. Strictly speaking, the term *vaccination,* from the Latin word *vacca* for a cow, should be limited to the use of vaccine lymph derived from the calf for protection against smallpox. But like many other words its meaning has broadened, and has come to signify not only the operation of implanting vaccine lymph on the skin, but the principle that lies behind it, namely of protection against an infectious disease by inducing a mild attack of the disease beforehand.

A further broadening has led to applying the term vaccination to the introduction into the body of dead micro-organisms or their products in place of living organisms, in the hope of stimulating the same sort of immunity as results usually from an attack of the disease in its normal or attenuated form.

Vaccination is merely one example of immunization—and it is doubtful whether the strict confinement of its use to protection against smallpox is any longer justifiable, particularly when vaccine lymph is now made from other animals than the calf, such as the sheep and the buffalo. I shall therefore use the term vaccination as synonymous with active immunization with live or dead micro-organisms or their products in an attempt to protect against any infectious disease.

The term *inoculation* is of narrower scope, and is best, though by no means always, reserved for the application to the surface of, or the injection into, the tissues of a living micro-organism, or the transfer of a living micro-organism to a culture medium of cells or of inanimate material. The term may be extended to the injection of dead organisms, in which case it can be used in place of vaccination. One speaks thus of inoculation against diphtheria, whooping cough or tetanus. It must be realized, however, that the terms inoculation and vaccination are not synonymous, since inoculation is often undertaken with the aim not of protecting against a disease, but of actually conferring it.

For the introduction of blood, serum, saline, or drugs into the tissues, that is to say of materials other than micro-organisms or their products, the term *injection* should preferably be used. The distinction between inoculation and injection I shall try to make, because I think the special meaning of the term inoculation is worth retaining. I shall probably be guilty, however, at times of using the word in its wider sense, and for this I

must beg the licence of inconsistency that should be accorded to all those who lay down rules about language.

To return to the purpose of these lectures, I regard it as fundamental that any doctor applying a remedy to a patient should be conversant, so far as possible, with its ill effects as well as with its good effects. This is doubly true when prophylaxis is concerned. Risks may be taken with a patient who is desperately ill or in danger of contracting some serious disease that should never be taken with a normal subject. It should be a rule in all prophylactic work that no harm should ever be unnecessarily inflicted on a healthy person.

The risks attendant on the use of vaccines and sera are not as well recognized as they should be. Indeed our knowledge of them is still too small, and the incomplete knowledge we have is not widely disseminated. This was forcibly brought home to me when I read a statement by a university lecturer in bacteriology at a symposium in 1965 on immunization, that the first recorded disaster associated with a vaccine was that known as the Lübeck tragedy. The failure of a health officer to appreciate the risks of immunization is regrettable enough, but that a medical bacteriologist should be wholly ignorant of the long series of accidents that occurred during the forty years before 1930 struck me as being almost incredible, till I reflected that his ignorance must be due to the almost complete absence of information on the subject in current textbooks of bacteriology. The lesson to be learnt is the importance of approaching any subject from a historical angle, for unless we know and can benefit from the mistakes of our predecessors we are liable to make even greater mistakes ourselves.

The woeful record I present of the accidents attendant on immunization and the ways in which they have arisen will not be complete. Far from it in fact. Even if I had had time to comb the whole of the relevant literature, I should still not have been in a position to give a complete record. This is mainly because a large number of accidents—I suspect the majority—have never been reported in print, either through fear of compensation claims, or of giving a weapon to the anti-vaccinationists, or for some other reason. Admittedly most of the larger accidents have been reported, but even with some of these attempts were made to keep knowledge of them from the public. Very few, however, of the sporadic accidents can have been published. The late Dr J. R. Hutchinson of the Ministry of Health collected records of fatal immunological accidents during the war years, and was kind enough to show them to me. I was frankly surprised, when I saw them, to learn of the large number of persons in the civil and military population that had died apparently as the result of attempted immunization against some disease or other. Yet only a very few of these were referred to in the medical journals.

When one considers that Dr Hutchinson's record covered only four or five years, and was limited to Great Britain, and that in other countries—in Europe, Asia, Africa, America and Australia—probably much the same proportion of accidents was occurring; and further, that such accidents have probably been going on for the last sixty or seventy years, one realizes what a very small proportion can ever have been described in the medical literature of the world.

I make no apology, therefore, for the incompleteness of my record. I am concerned more with the mechanism by which immunological accidents have occurred than with their numbers. Improvement will come

not from considering the magnitude of these accidents but from the way in which they might have been avoided.

Though I make mention in places of Dr Hutchinson's records, I have compiled my figures almost entirely from published papers. With one or two small exceptions I have not included the unpublished records of the Ministry either before or since the second world war. I have, however, when published accounts were deficient or absent, made use of private information with which I have been supplied and of reports which, though confidential at the time, can no longer be regarded as such.

During the course of my reading I have come to the conclusion that no vaccine or antiserum can be regarded as completely safe. Some are very much safer than others, but no vaccine or antiserum that has yet been used has been free from complications or accidents of one sort or another. When possible, I have endeavoured to assess the degree of probable danger; but too often I have failed through lack of exact information on the number of persons affected and the number exposed to risk. Unless both the numerator and the denominator are known, quantitative assessments may fall wide of the true mark. Moreover, the risk, even for a single vaccine, is not uniform. It varies, among other things, with the immunological status and behaviour of the population concerned.

The fact that all forms of active and passive immunization are potentially dangerous is no condemnation of their use. Though I do not intend to weigh up the advantages and disadvantages of each type of vaccine or antiserum—partly because it would carry me beyond the scope of my present task and partly because of the insufficiency of our knowledge which I have just stressed—it is fair to conclude that most of the well-known protective immunological agents that we use do a great deal more good than harm. The complications and accidents for which they are from time to time responsible must be looked upon as the price we pay for the protection these agents confer upon us. There is no insurance without a premium. Our business is to provide a greater and more comprehensive insurance and to diminish the size of the premium.

With this in mind I propose to draw attention to the various complications and undesirable sequelae of immunization. They are numerous in both kind and frequency; and I hope that the information I provide will sharpen the awareness of medical men to the potential danger of vaccination and cause them sometimes to think twice before incurring a risk that may well prove disastrous.

I restrict myself to man, and do not propose to deal with the wide range of immunizing products used for animals, or with the ill effects of blood transfusion or drug administration, or with the accidents common to all injections, such as a broken needle, contamination of the puncture wound, fainting or shock in the subject under treatment, or laceration of the tissues that may result from the use of a high-pressure jet type of injector (see Lenz 1966).

2

CLASSIFICATION OF ACCIDENTS AND COMPLICATIONS

BEFORE DESCRIBING the complications of vaccination, I must attempt some form of classification. This is very difficult, and I have failed to devise any entirely satisfactory system.

Figure 1 shows merely a list of the common vaccines and antisera classified according to their nature.

I have divided them primarily according to whether they relate to bacteria or viruses. Vaccines are subdivided into live or dead, and the dead into the nature of the product employed. Antibacterial sera are prepared against whole organisms or their toxins; antiviral sera against only the whole virus.

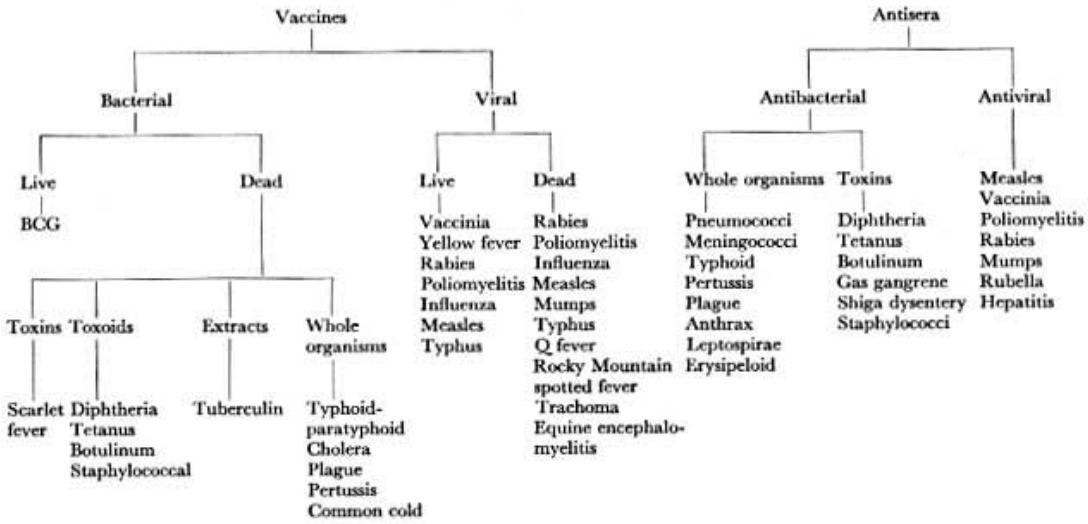

FIG. 1. Classification of vaccines and antisera.

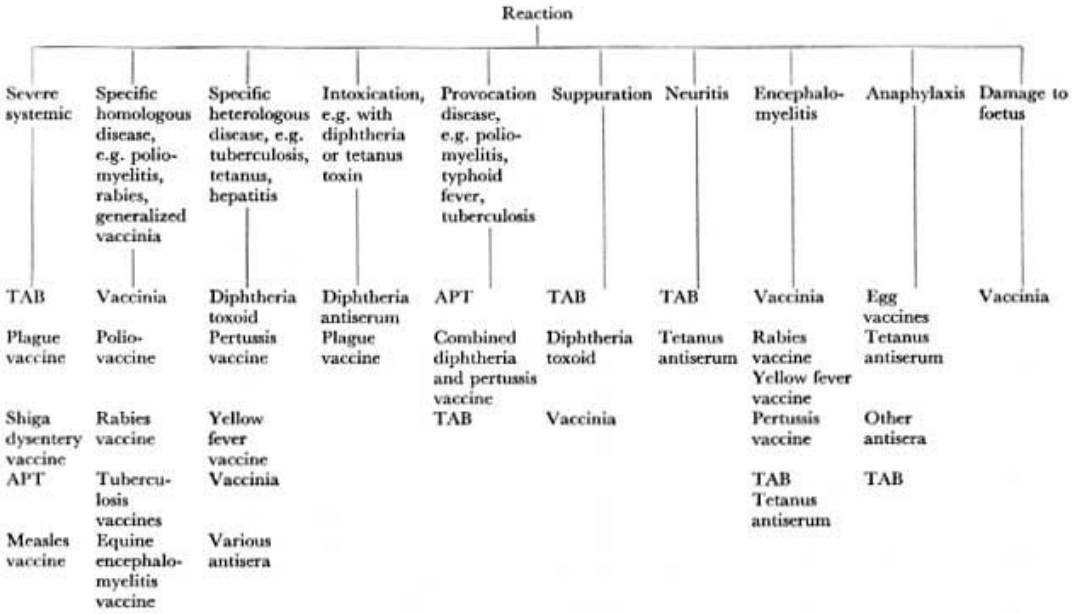

FIG. 2. Classification of complications and accidents according to the nature of the immunizing agent used.

In Figure 2 the various complications and accidents are classified according to the nature of the immunizing agent used. This is useful in indicating what sort of vaccines or antisera may give rise to what sort of complications but is otherwise not very illuminating. The variety of complications is wide and ranges from a severe but transitory disturbance of health to acute or chronic disease sometimes proving fatal. Indirectly the foetus may be affected.

A better method of classification is depicted in Figure 3, in which the complications are classified according to their probable causation. This provides more valuable information than Figure 2, but is open to the objection that our knowledge of causation is still incomplete and that therefore a certain amount of guesswork is unavoidable. Moreover, the allocation of some of the complications to a particular category is bound to be arbitrary.

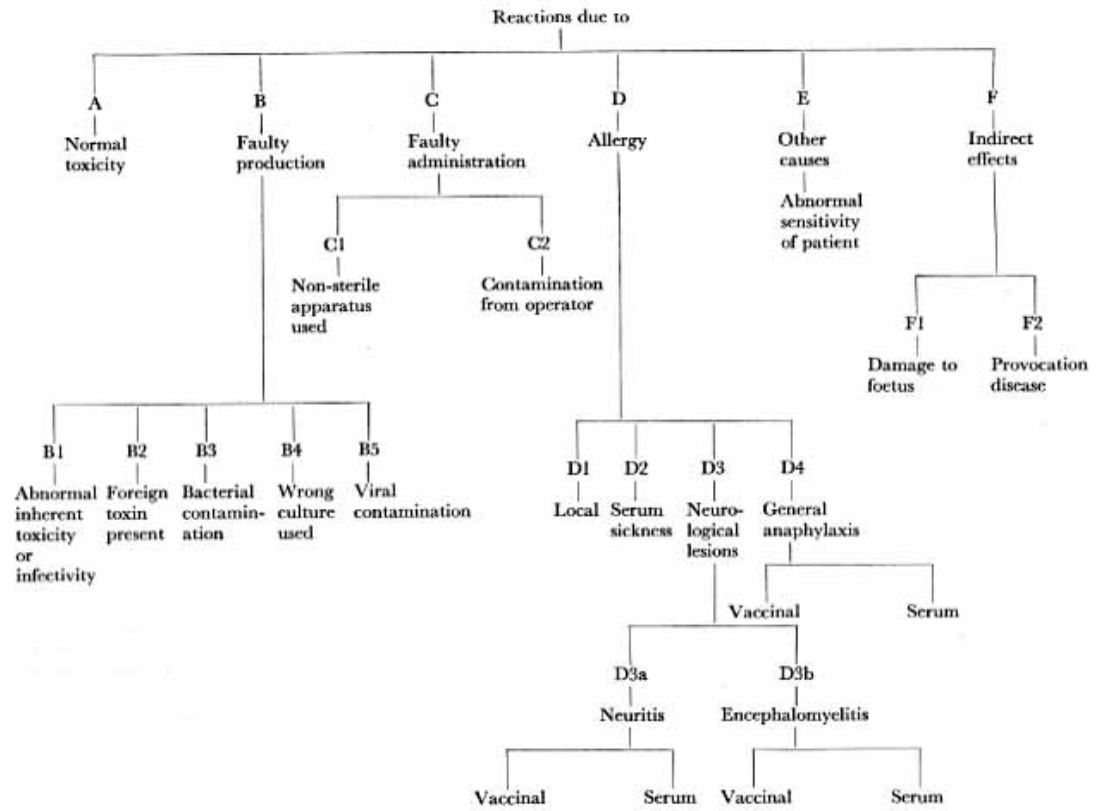

FIG. 3. Classification of complications and accidents according to their probable causation.

Should, for example, bacterial pyrogens be grouped under 'inherent toxicity' or 'bacterial contamination'? Is it fair to include 'neurological lesions' under 'allergy'? Should severe and sometimes fatal reactions after TAB vaccine be regarded as due to 'normal toxicity' or to abnormal sensitivity of the patient? And what criteria are to be used for distinguishing abnormal sensitivity of the patient due to other causes from that due to allergy as understood by the immunologist?

More important than the niceties of classification is the difficulty of deciding whether a given complication is the result of the vaccine or merely coincidental. How, for instance, is it possible to tell whether six cases of neurological damage occurring after the vaccination of 2½ million people are to be ascribed to the vaccine? Without a control group, it is often impossible to say. Exact diagnosis, particularly when supported by histological findings at autopsy, may help; but only too often, particularly with neurological lesions in children, exact diagnosis is lacking. The most I can do is to record the findings and indicate where the relation of cause and effect seems to me to be doubtful.

For purposes of reference Figures 2 and 3 are combined in Table 1, which shows not only the mode of causation of any given complication, but also the type of protective agent responsible for it.

In the following chapters mention will be made of each of the various accidents and complications depicted in this table.

TABLE 1. Complications and accidents classified according to probable causation and nature of agent involved

Probable causation	Nature of complication	Nature of agent concerned
A. *Normal toxicity*	Severe local and constitutional reaction	TAB, plague vaccine, APT, measles vaccine, Shiga dysentery vaccine
B. *Faulty production*		
B1 *Abnormal inherent toxicity or infectivity*	Diphtheritic intoxication	Diphtheria prophylactic
	Tetanus	Tetanus toxoid
	Rabies	Rabies vaccine
	Poliomyelitis	Poliomyelitis vaccine
	Equine encephalomyelitis	Equine encephalomyelitis vaccine
	Measles	Live measles vaccine
	Meningo-encephalitis	Yellow fever vaccine
	Syphilis	Human vaccine lymph
B2 *Foreign toxin present*	Tetanus intoxication	Diphtheria antiserum
B3 *Bacterial contamination*		TAB
		Diphtheria TAM
	Staphylococcal abscess	Tuberculin
		Measles antiserum
		Vaccinia
		Plague vaccine
	Tetanus	Diphtheria antiserum
		Vaccinia
	Tuberculosis	Measles antiserum
	Severe constitutional reaction caused by pyrogens	TAB
		Stock vaccines
B4 *Wrong culture used*	Tuberculosis	BCG (Lübeck)
B5 *Viral contamination*		Yellow fever vaccine
	Hepatitis	Measles antiserum
		Mumps antiserum

TABLE 1—*continued*

Probable causation	Nature of complication	Nature of agent concerned
C. *Faulty administration*		
C1 *Use of non-sterile apparatus*	Tuberculosis	Diphtheria TAF Diphtheria-tetanus toxoid
	Staphylococcal toxaemia	Diphtheria toxoid
	Streptococcal abscesses	Diphtheria TAM
	Hepatitis	TAB
C2 *Contamination from operator*	Tuberculosis	TAB Pertussis vaccine Diphtheria APT
	Streptococcal abscesses	Diphtheria APT Diphtheria TAM Diphtheria TAF
D. *Allergy*		
D1 *Local allergy*	Cyst formation	APT Alum-precipitated pertussis vaccine Oily influenza vaccines
	Arthus phenomenon	Diphtheria TAM Tetanus toxoid Tetanus antiserum Staphylococcal vaccines
D2 *Serum sensitivity*	Serum sickness	Diphtheria antiserum Tetanus antiserum Other antisera
D3 *Sensitivity of nervous system*	D3a Neuritis	
	Post-vaccinal	TAB
	Post-serum	Tetanus antiserum
	D3b Encephalomyelitis	
	Post-vaccinal	Vaccinia Rabies vaccine Pertussis vaccine Typhoid fever vaccine Poliovaccine
	Post-serum	Tetanus antiserum
D4 *General anaphylaxis*	Acute anaphylactic reaction, sometimes fatal	Various vaccines Tetanus antiserum Diphtheria antiserum Streptococcal antiserum Pneumococcal antiserum

E. *Other causes*		
Abnormal sensitivity of patient	Tuberculosis	BCG
	Lupus	Vole vaccine
	Generalized vaccinia Eczema vaccinatum Chronic progressive vaccinia	Vaccinia
	Miscellaneous reactions and death	TAB Pertussis vaccine Stock vaccines Yellow fever vaccine Rabies vaccine
F. *Indirect*		
F1 *Damage to foetus*	Abortion or congenital abnormalities	Vaccinia
F2 *Provocation disease*	Poliomyelitis	APT Combined diphtheria-pertussis vaccine
	Tuberculosis	TAB Stock vaccines Tuberculin
	Typhoid fever	TAB
	Trench fever	TAB

3

NORMAL TOXICITY: SIMPLE REACTIONS TO BACTERIAL VACCINES

AS ALREADY mentioned under Classification it is sometimes difficult to decide into which category a given reaction should be put. Where to draw the line between a simple and a complicated reaction must to some extent be a matter of individual opinion.

For practical purposes a simple reaction may be defined as one that is experienced in greater or less degree by the majority of persons receiving the vaccine, is attended by local and constitutional disturbance lasting not more than a few days, and causes no local destruction of tissue or general manifestations other than those common to a febrile illness. To put it more negatively and more specifically it is a reaction that is free from suppuration or from invasion with extraneous micro-organisms, is accompanied by neither abscess formation nor ulceration, is not characterized by toxaemia, by local or general anaphylactic phenomena, or by serious disturbance of the cardiovascular, nervous, skeletal, genito-urinary or other main system of the body, is never fatal, and leaves behind it no disability.

These definitions are imperfect and need some elaboration. For example, the statement that the reaction is experienced in greater or less degree by the majority of persons receiving the vaccine refers to a normal properly prepared vaccine. Limitation of the disturbance caused by the vaccine to a few days is true of dead vaccines but not of all live vaccines. Smallpox vaccine, for instance, gives rise to skin lesions lasting for 3 weeks, accompanied too by some degree of destruction and ulceration of tissue; but this is the reaction experienced by most normal persons. Not till it exceeds this and causes progressive ulceration, generalized vaccinia, or neurological manifestations can the reaction be regarded as complicated. The reaction to live measles vaccine ranges from minor constitutional disturbance to a genuine attack of measles, modified though it is in its severity (see Katz *et al. 1*960, Goffe *et al.* 1963). Should this be considered a simple or a complicated reaction? Because it is seen in a fair proportion of subjects receiving the vaccine and because it is neither accompanied nor followed by other manifestations of disease, it is probably best regarded, like the response to smallpox vaccine, as a simple reaction. BCG vaccine generally gives rise to a trivial degree of ulceration of the skin, which may be regarded as a normal reaction; but when this is accompanied or followed by severe lymphadenitis, generalized invasion of the body, erythema nodosum, or lupus vulgaris the reaction must be classified as complicated.

Ignorance of the exact cause of the reaction adds to the difficulty of classification. Sterile abscess formation or, as some prefer to call it, cyst formation is a case in point. This is liable to occur after the injection of vaccines containing alum or various oily adjuvants and is seen in only a minority of injected subjects. Partly because of this and partly because there is reason to believe that it is a manifestation of allergy, it is perhaps best classified as a complicated reaction.

CLINICAL MANIFESTATIONS OF A SIMPLE REACTION

Locally a simple reaction is characterized by a variable degree of inflammation manifesting itself within a few hours. The site of injection is red, sometimes swollen or indurated, mildly painful and tender. The limb is stiff and uncomfortable, and there may be some lymphangitis and enlargement of the regional lymphatic glands. When the reaction is severe the redness and swelling may spread for several inches around the site of injection; and when very severe the whole arm from shoulder to wrist may be red, swollen, painful, and so stiff as to make movement almost impossible. Usually regression occurs in a day or two and the arm returns to normal, but severe reactions may take four or five days to subside.

Constitutionally the reaction is characterized by fever—seldom above 100 or 101°F—malaise, mild aching of the back and limbs, headache, apathy, anorexia, and sometimes vomiting. It comes on within a few hours of injection, reaches its height in 24 to 48 hours, and then gradually disappears. With most reactions the subject is able to carry on with his usual duties, but with severe reactions he is confined to bed for one or two days, much as in a mild attack of influenza.

FACTORS AFFECTING THE REACTION

The *nature* of the organism is one of the major factors affecting the incidence and the degree of the reaction. Typhoid-paratyphoid (TAB) vaccine is one of the most potent of the vaccines in common use, cholera vaccine and tetanus toxoid are among the least potent, and pertussis vaccine comes in between. The toxicity of the vaccine is determined mainly by the chemical constitution of the organism, such as the lipopolysaccharide of the typhoid bacillus or the phosphatide fraction of the tubercle bacillus. Shiga dysentery vaccine and some plague vaccines have proved so toxic that their use has had to be discontinued.

The constitution of the vaccine likewise plays a part. Vaccines containing alum, such as the alum-precipitated toxoid (APT) of the diphtheria bacillus, give rise to a greater reaction than do vaccines containing simple formolized toxin; but on the other hand, aluminium phosphate may lessen the reaction to a saline influenza virus vaccine. Emulsified vaccines in mineral oil are slowly absorbed and occasionally give rise to a chemical abscess, but on the whole cause less reaction than plain saline vaccines. Combined vaccines, provided they are given in the same total dosage, are not necessarily more toxic than single vaccines. The reaction they elicit is determined by the most toxic component of the vaccine; but when containing alum some of them are liable, as with combined diphtheria-pertussis vaccine, to lower the resistance of the body and lead to activation of a latent infection—the so-called provocation effect (see p. 265).

Lenz (1966) is of the opinion that alum itself is irritant and that alum-containing vaccines should always be given intramuscularly. He notes the case of a soldier who had a chronically draining wound for over a year after jet injection of alum-precipitated tetanus toxoid by a Hydrospray. The jet type of injector cannot be relied on to secure intramuscular deposition of the vaccine and should therefore not be used with a vaccine containing alum. Moreover when a syringe is used, the needle should be wiped before injection to avoid contaminating the fatty tissues with alum.

Vaccines made from viruses grown in eggs may cause a reaction in persons who are sensitive to egg protein; and vaccines given repeatedly may sensitize the subject to some constituent of the organism or of the

medium in which it is suspended. Similarly vaccines containing horse serum, such as the toxoid-antitoxin floccules (TAF) of the diphtheria bacillus, may cause a reaction in persons who are sensitive to horse serum. All these are examples of allergy (see p. 136).

The reaction tends to vary according to the route of injection. Alum-precipitated vaccines and vaccines emulsified in mineral oil are best injected intramuscularly. Intradermal injection of TAB vaccine gives rise to less reaction than subcutaneous, even when the same dosage is used. The severest reactions occur after intravenous injection. This route is intentionally chosen when it is desired to produce protein shock for therapeutic purposes.

The volume of the vaccine given determines the amount of pain caused by the injection. Lepine (1961), for example, found that the immediate discomfort was less after injecting 40 000 X 10^6 pertussis bacilli in 0.5 ml than 20 000 X 10^6 in 1 ml. The local and general reactions after 24 hours were, however, the same, indicating that the immediate discomfort was due to distension of the tissues.

On the whole the arm is preferable to the thigh (Gray and Cartwright 1952) and is less liable to go septic. The buttock is best avoided and, when large quantities have to be injected, as with rabies vaccine, the loose tissue of the abdomen is to be chosen.

Infants and young children generally react less than older children and adults. This may be partly dependent on the absence of allergy to the usual constituents of vaccines during the early years of life.

Reactions are often very capricious. Sometimes a given subject will react severely to a first injection, but not to a second given a week or two later. Another subject will react to the second injection but not to the first. Another will react to both, and another to neither. With so many different factors affecting the occurrence and degree of reactions, it is manifestly impossible to give any figures for incidence. Each vaccine must be considered individually. Even so, the difference between different populations and different observers is so great that comparison of figures is often misleading. When the toxicity of different vaccines is to be compared, then a more or less homogeneous population must be studied and all reactions must be read and recorded by a single observer. (For reactions to various vaccines see Edsall 1946, Report 1966.)

4

FAULTY PRODUCTION: INHERENT TOXICITY OR INFECTIVITY

INHERENT TOXICITY

NEARLY ALL the recorded incidents in which the vaccine has proved to be inherently toxic have followed the use of prophylactic agents against diphtheria, and nearly all have been associated with the injection of toxin-antitoxin mixture (TAM). This particular form of prophylactic agent was the first to be generally employed for active immunization against diphtheria; and it so happens that, owing to the great care required in its preparation—particularly in the exact degree of underneutralization of the toxin and to the instability of the mixture—it is one of the least satisfactory agents to use. After a number of accidents had occurred, it was realized that diphtheria toxin was too dangerous a substance to be used for human injection, even when it was neutralized with antitoxin.

The introduction of formolized toxin by Glenny and his colleagues in Britain (Glenny and Südmersen 1921, Glenny and Hopkins 1923), and by Ramon in France (1923, 1928) under the name of anatoxin, changed the picture, because it made possible the substitution of toxoid for toxin. The finding that formol toxoid (FT) alone was a good immunizing agent rapidly led to the abandonment of the toxoid-antitoxin mixture, which is now used only in the form of toxoid-antitoxin floccules (TAF) for the immunization of adults or of other persons who are likely to react too strongly to formol toxoid or to alum-precipitated toxoid (APT).

Since the discontinuance of toxin-antitoxin mixture few accidents have been recorded as the result of diphtheria immunization ; though, as the very serious accident at Kyoto in 1948 showed (see p. 38), trouble may still occur from failure to control adequately the process of formolization in the preparation of toxoid.

The incidents recorded in this chapter are summarized in Table 2.

TABLE 2. Inherent toxicity or infectivity of vaccines

Type of illness	Vaccine	Incident	Number affected	Number of deaths
Diphtheritic intoxication	TAM	Dallas, Texas, 1919	120 or more	10
Diphtheritic intoxication	TAM	Belgium 1922	1	1
Diphtheritic intoxication	TAM	Concord and Bridgewater, Mass., 1924	43	0
Diphtheritic intoxication	TAM	Baden 1924	17	7
Diphtheritic intoxication	Anatoxin	Tashkent 1926	14	12
Diphtheritic intoxication	Anatoxin	Medellín, Colombia, 1930	48	16
Diphtheritic intoxication	Anatoxin	Italy 1933	Several hundred	over 30
Diphtheritic intoxication	APT	Kyoto, Japan, 1948	606	68
Tetanus intoxication	Tetanus toxoid	Europe	not known	not known
Poliomyelitis	Kolmer's Poliomyelitis	USA 1935	10	5
Poliomyelitis	Brodie's Poliomyelitis	USA 1935	2	1
Poliomyelitis	Cutter's Poliomyelitis	USA 1955	260 including contacts	10
Poliomyelitis	Lederle-Cox poliomyelitis	West Berlin 1960	?25	
Meningo-encephalitis	Yellow fever	Several, mainly in West Africa and Brazil	Several hundreds	not known
Encephalomyelitis	Venezuelan equine encephalomyelitis	1954	14	0
Rabies	Rabies, Pasteur's or Högyes	Miscellaneous	at least 30	30
Rabies	Rabies, Fermi's	Fontaleza, Ceará, Brazil, 1960	18	18

DIPHTHERIA PROPHYLACTIC: FREE TOXIN IN THE VACCINE

Dallas, Texas, 1919

This incident will be described in some detail, not only because it was chronologically the first occasion on which prophylactic vaccination against diphtheria led to a number of fatalities, but also because, owing to unusually well-documented private information, it is possible to report fairly fully on the effect of free toxin on non-immune children.

The city of Dallas began administering diphtheria toxin-antitoxin mixture (TAM) on 23 October 1919. Between that date and the 12th November over 300 injections were made by the Emergency Hospital without any ill effect; but a number of injections given on the 12th and 13th November, both by private and municipal physicians, were followed by a severe reaction. These were all traced to the use of a particular batch of TAM prepared by one manufacturer. Other batches prepared by the same manufacturer and by different manufacturers proved harmless.

There appears to be no record of the total number of children receiving the toxic batch. According to one report (Report 1919), several hundred doses were given, and 40 severe reactions followed. The medical officer of health stated that over 50 severe reactions were reported; but the real number must have been much higher, because a special study was made of 120 cases which presumably did not include all of those that occurred. Of these 120 cases, 96 had local and constitutional reactions; the others were presumably immune to diphtheria and suffered no ill effect. Among the 96 reactions, 10 were very severe and resulted in death; 74 were severe, and 12 were moderate. Seven of the ten children that died succumbed during the phase of acute toxaemia, that is within about a fortnight; the other three died of paralysis affecting the muscles of respiration and possibly the heart 31, 39, and 46 days after the injection.

Dr W. H. Park, who was asked to test the toxic batch of vaccine, reported on 5 December that he had found free diphtheria toxin present in

an amount over 50 times as great as the permissible amount; even 0.1 ml of the product proved fatal to a 250-gram guinea-pig. Though no post-mortem examination was made on any of the fatal cases, there is every reason to believe that death was due to specific diphtheritic toxaemia.

The children injected ranged from 1 to 18 years of age, but the fatal cases were all in children of 1 to 5 years. Eleven of these children were given 1000 units of antitoxin between 3 and 15 days after the injection. Five of the eleven died, two of whom were practically moribund at the time. In the remaining six the antitoxin was considered to have had a beneficial effect in decreasing the severity of the local reaction and promoting healing of the ulcerated area.

Clinical history. The clinical histories in the series of 96 cases were practically uniform. The first symptom was an intense burning observed immediately at the site of injection. This increased in severity during the next two to eight hours till it became an agonizing pain. It was accompanied by localized swelling and, as a rule, nausea and vomiting. The swelling started at the site of injection over the insertion of the deltoid muscle, and rapidly spread both upward and downward. The arm and forearm increased to two or three times their normal size, and the wrist, hand and fingers were affected. In the upward direction the swelling involved the shoulder girdle, and to a less extent the cervical region. In some children it passed over to the chest and back on the opposite side of the body. The generalized swelling was accompanied by acute lymphangitis, with reddened inflammatory streaks having a sharp line of demarcation extending in all directions from the site of injection. The swelling began to subside about the 6th or 7th day and receded fairly rapidly.

About 24 to 48 hours after the injection vesicles appeared in the swollen area resembling pemphigus. They ruptured, partly discharged a fluid having a burning effect on the normal skin, and refilled again. The fluid itself was sterile. The swelling and the vesicular eruption subsided simultaneously, leaving a raw denuded area 6-12 or more square inches in size, the centre of which was occupied by a ragged, ill-smelling, gangrenous mass of tissue which later sloughed off. The separation of the slough left a painful granulating area that persisted for 2 to 2½ months before healing and closure of the wound began.

Of the constitutional symptoms the two most distressing were vomiting and constipation. The vomiting was periodic or cyclic, was excited by attempts to give either food or drugs, and continued till the local swelling had subsided. Constipation was obstinate, and difficult to treat because of the vomiting. It appeared early and lasted for 3 to 4 months. The temperature was raised to 101° or102°F, the heart rate was accelerated, the urine contained albumin and casts, and the leucocytes in the blood reached 12 000 to 24 000 per cmm.

The later clinical manifestations can best be described under the different systems.

Circulatory system. About the 9th or 10th day the heart began to show signs of distress. The rate became rapid, from 130 to 150 beats per minute, and the rhythm irregular with alternate slowing and acceleration. The cardiac signs lasted from the middle of the 2nd to the end of the 8th or 10th week, irregularity of the rhythm being the last sign to disappear. The pulse pressures were all within the normal range and the responses to

functional tests were normal, suggesting to the observers that the cardiac symptoms were of vaso-motor rather than of myocardial origin.

Neuromuscular system. All patients suffered from partial paralysis affecting one or more muscle groups. The ciliary muscles were first affected, leading to blurred vision and widely dilated pupils. This started about the middle to the end of the 3rd week, and was followed in order by palatal paralysis in the 4th week, paralysis of the respiratory muscles from the 3rd to the 6th week, of the extrinsic eye, cervical and back muscles in the 6th week, the arm and hand muscles in the 6th to 7th week, the muscles of the eyelids in the 7th week, the tongue muscles in the 8th week, and the muscles of the lower limbs in the 8th to 9th week. Every patient showed loss of the power of accommodation, absent knee jerks, a partial paralysis of the lower limbs, and tenderness of the intercostal, brachial, radial, and posterior tibial nerves. Apart from occasional numbness, tingling or itching there was no disturbance of the sensory nerves. The mind remained active and alert, even in the fatal cases.

The symptoms referable to the neuromuscular system, after remaining unchanged for about three weeks, disappeared in the order of their onset and at much the same rate. On the average recovery took 18 to 20 weeks.

In general the nerves affected were those concerned in the motor functions, the sympathetic system being primarily attacked and the general nervous system secondarily. The extensor groups of muscles suffered more than the flexor. A striking feature was the inverse relation between the local reaction and the paralytic sequelae. The older patients, who were not confined to their beds, showed a greater degree of paralysis than those treated by absolute rest.

Some children suffered from the 5th to the 7 th week from a skin eruption resembling herpes zoster, particularly around the larger joints and on the extensor surfaces.

Review. There seems no doubt that this mishap was due to the presence in one particular batch of TAM of free diphtheritic toxin. Investigation at the factory did not reveal what had gone wrong, or, if it did, the nature of the mistake was never disclosed. There may have been a fault in labelling or in the records of the tests, but all that is certain is that this particular batch contained free toxin. It may be, as Forbes (1927) asserts, that in process of preparation toxin was added to the antitoxin in two separate portions, thus ignoring the Danysz phenomenon. Unfortunately Forbes does not say where he got this information from, and, as I have been able to find no other record of it, it must be regarded as unconfirmed.

Belgium 1922

This incident, which affected only one child, is not fully documented, and the description given here, based partly on published papers (Boeckel 1928) and partly on private information, is regrettably incomplete.

During an immunization campaign in Belgium at the beginning of 1922 a child of 14 years was injected subcutaneously by mistake with 1 ml from an ampoule containing diphtheria toxin that had apparently got into a batch of toxin-antitoxin mixture by mistake. The toxin was one having a minimal lethal dose for a 250-gram guinea-pig of 0.01-0.008 ml. The child must therefore have received rather over 100 guinea-pig MLD.

Two to three hours after the injection the child experienced severe local pain. By the following day there was a reddish-violet swelling

around the site of injection, which continued to increase till the sixth day. Constitutional symptoms were severe during the first two days but began to subside after the third day. The child died on the seventh day from cardiac paralysis.

Concord and Bridgewater, Massachusetts, 1924

Briefly, two lots of diphtheria TAM, prepared by the Massachusetts Antitoxin and Vaccine Laboratory, that had passed satisfactorily the usual laboratory tests gave rise on injection into children at Concord and Bridgewater to severe local and constitutional reactions, none of which however proved fatal. The two lots in question, portions of which had been used uneventfully during the previous week, had become toxic in the meantime, apparently as the result of freezing during the cold weather that prevailed at the time (Report 1924). More fully, the facts were as follows.

Concord

On Monday 21 January 1924, four 20 ml bottles of lot 100 T containing 1 L+diphtheria toxin-antitoxin mixture were shipped from Boston to the Board of Health at Concord where they were received the next day. During transit there is every reason to suppose that the package was exposed to a temperature several degrees below freezing. On arrival the material was stored in the refrigerator. On the morning of Tuesday the 29th four vials, after thawing of the frozen contents, were used by a private practitioner to inject 23 children at the local academy. The dose given was 1 ml. That evening 21 of the children were disturbed and slept badly. The following day they were suffering from general malaise, fever, vomiting, and tenderness of the arm. The two children who did not react abnormally had received one or two doses of TAM some weeks previously and had presumably become immune as a result.

The local reaction consisted of initial pain at the site of injection followed several hours later by painful swelling and redness. The injections had been made at the insertion of the deltoid muscle. When inspected four days later by Professor Zinsser, the arms were swollen to nearly twice their normal size, and the skin was deep red and tense with oedema extending from the shoulder to just below the elbow. In some children the oedema, though not the redness, reached the neck and chest above and the hand and fingers below. The oedema was still spreading after four days. In a few cases the area around the injection site showed evidence of incipient necrosis, and in many cases large blebs up to three inches or more in diameter, filled with a yellowish fluid, were evident.

More generally, the pulse was rapid, the mental state alert, the pupils were somewhat dilated but reacted to light, the patellar reflex was exaggerated or practically absent, and there was severe constipation.

On Professor Zinsser's recommendation it was decided not to give antitoxin, mainly because it was doubtful whether after four or five days it would be of any value in neutralizing toxin that had already been fixed to the tissues, and partly to avoid adding to the children's distress by causing serum sickness.

The outcome was satisfactory. The constitutional symptoms subsided and the local reactions gradually disappeared (Kelley 1924).

The batch of TAM used was from a lot of 240 vials each containing 20 ml and of 1580 ampoules each containing 1 ml. It had been prepared according to the method recommended by the United States Hygienic Laboratory. Five vials had been sent to the Hygienic Laboratory at

Washington and had passed satisfactorily the usual laboratory tests. Altogether 225 vials and 1327 ampoules, exclusive of the Concord shipment, had been distributed throughout the state and had nowhere caused any untoward reactions. In Worcester approximately 1700 doses of 1 ml had been used satisfactorily during the previous week. It may therefore be concluded that there was nothing wrong with the batch when it left the State House at Boston.

Bridgewater

On Monday 28 January 1924, 31 children were injected with 1 ml of TAM lot 100 M. Of these, 22 children had unusually severe reactions. Eight of the 31 children, who were receiving their first injection, all reacted severely; of 22 who were receiving their second injection, 14 reacted; and one child who was receiving a third injection failed to react. The 22 children receiving their second injection had been injected with material from the same lot ten days previously without any abnormal sequelae, indicating that the TAM had become toxic during this interval. Inquiry showed that it had frozen during the cold spell and that it had been necessary to thaw the frozen material before use. The reactions in the children were substantially the same as those recorded in the Concord children.

EXPERIMENTAL OBSERVATIONS

The fact that both at Concord and at Bridgewater the toxin-antitoxin mixture had become frozen as the result of exposure to an unusually low temperature suggested that freezing might lead to a dissociation of the mixture and to inactivation of the antitoxin, leaving free toxin in the fluid. Experiments to test this tentative explanation were immediately set in hand.

Experiment 1. Three vials from the reserve stock of the Antitoxin and Vaccine Laboratory containing 1 L+TAM, lot 100 T—the same lot as that used at Concord—were placed in a refrigerator at 8°F. One vial was removed after 3 hr 35 min and was found to be frozen solid. When thawed slowly at room temperature, the fluid was seen to be perfectly clear. Another vial was removed after 18 hr 25 min, and on inspection showed a creamy-white deposit at the ice-air interface. When it was thawed, some translucent gelatinous particles were observed in the fluid together with some opaque particles that had flocculated and settled to the bottom.

Injection into guinea-pigs showed that (a) lot 100 T was within the limits of toxicity approved by the US Hygienic Laboratory; (b) exposure to a temperature of 8°F for about 3½ hours caused no increase of toxicity in this product; (c) exposure to a temperature of 8°F for 18 hours caused about a tenfold increase in toxicity. Examination of an unopened vial from the toxic batch at Concord showed that it was five times more toxic than the unfrozen material; it contained in 1 ml slightly less than 1 guinea-pig MLD—enough to account for the reactions observed in the Concord children.

Experiment 2. The contents of a vial of lot 100 T that had been frozen at 8°F for 18½| hours were injected into guinea-pigs with and without concurrent diphtheria antitoxin. As before, the frozen product proved acutely toxic, whereas no toxicity was observed when it was injected

along with antitoxin. This indicated that the toxicity of the frozen product was due to specific diphtheria toxin and not to some other toxic agent.

Experiment 3. This experiment was carried out with a different batch of TAM, lot 100 X, made from the same toxin and antitoxin as lot 100 T. The results showed that it too became toxic on freezing. The longer the freezing period, up to 120 hours, the greater was the increase in toxicity. It was also found that, on removal of the flocculated sedimented antitoxin, the fluid had a greatly heightened toxicity.

Experiment 4. In this experiment another lot of 1 L+TAM, lot 100 Z, made from a different toxin and antitoxin from those used for 100 T and 100 X, was frozen for varying lengths of time and injected into guinea-pigs. An exposure of 6 hours led to a slight increase in toxicity. Longer exposures led to a greater increase. This experiment made it clear that the effect of freezing was not peculiar to one particular lot of TAM.

Experiments 5 *and 6.* These experiments were made with batches of 3 L+TAM and 1/10 L+TAM. Both of these mixtures showed some increase in toxicity on prolonged freezing, but not as much as with the 1 L+mixtures.

Experiment 7. The purpose of this experiment was to determine the effect of freezing on solutions of antitoxin. It was found that concentrated antitoxin containing 10 000 units in each package showed only a slight increase in turbidity, whereas a 1/100 and a 1/2400 dilution in saline showed the formation of opaque insoluble particles which separated from the diluent. No observations appear to have been made to find out whether the particles passed into solution again on thawing and, if so, whether the resulting solution revealed any loss of antitoxin potency.

The general results of these experiments may be summarized by saying that freezing of a toxin-antitoxin mixture leads to dissociation of the two components, resulting in a partial flocculation of the antitoxin and an increase in the toxicity of the mixture as a whole; that the degree of toxicity increases with the duration of freezing; and that the phenomenon is much more strikingly exhibited by 1 L+ than by 3 L+ or 1/10 L + mixtures (Kelley 1924).

Further study of the effect of freezing on TAM

The Concord and Bridgewater experience attracted the attention of other workers. Glenny, Pope, Waddington and Wallace (1925) in Great Britain found that on prolonged storage at temperatures above freezing no substantial increase in toxicity occurred in toxin-antitoxin mixtures or any diminution in antigenic potency. The effect of freezing varied according to the composition of the mixture. They agreed with the American workers that under certain conditions the mixture became more toxic on freezing, but they were not satisfied with their explanation. They studied the possible role of phenol in the reaction. Certain strengths of phenol, round about 5 per cent, caused a greater relative destruction of diluted antitoxin than of toxin; and the addition of this concentration of phenol to a toxin-antitoxin mixture sometimes rendered it toxic. They formed the opinion that the local concentration of phenol that occurs when mixtures are frozen probably has a similar effect.

In a further communication two years later Pope (1927) showed that phenol might separate from a 0.5 per cent solution when frozen, the extent of separation depending on the protein and salt content of the toxin or antitoxin solutions, the temperature of freezing, and the duration of freezing. In certain circumstances a critical amount of phenol might separate from a TA mixture, causing a greater relative destruction of antitoxin than of toxin and rendering a non-toxic mixture toxic. Apart from TAM, Pope advised against the use of phenol or tricresol for the preparation of reagents used in the schick and the schultz-charlton tests.

Robinson and White (1928) in the United States, after pointing out that White and Robinson (1924) were the first to report the dissociation of diphtheria toxin-antitoxin mixtures on freezing, brought evidence to show that, on freezing a 1 L+TA mixture, the antitoxin was precipitated, even in the absence of phenol, but apparently went into solution again when left at **a** temperature above freezing. Thus, a mixture which became toxic on freezing might lose most of its toxicity when left for a time at room temperature, but again become toxic if it was frozen for a second time. Dissociation was observed only with 1 L+TA mixture, not with 3 L+ or 1/10 L+ mixtures. They concluded that, with certain mixtures such as the 1 L + mixture, the increased toxicity observed on freezing was due to dissociation rather than to destruction of antitoxin. They did not deny that phenol might have some effect, but they paid little attention to it.

CONCLUSION

Summarizing the evidence obtained by observation on the children at Concord and Bridgewater and by experimental work in the laboratory, it would appear that freezing for a sufficient length of time of 1 L+, but not of 3 L+ or 1/10 L+, toxin-antitoxin mixtures leads to an increase in toxicity. This is due to dissociation of the mixture with partial precipitation of the antitoxin, which is thus rendered unavailable for neutralization of the free toxin in the fluid. Whether the precipitated antitoxin undergoes any diminution in its potency and, if so, whether this is due to the effect of phenol in the mixture or to some other cause, remains doubtful.

McCoy, Rosenau and Park (1924) drew attention to the fact that, as experiments showed later, only certain TA mixtures became toxic on freezing, and that several hundreds of children in Boston, New York, and Washington had been injected with frozen preparations (probably 1/10 L + mixtures which were then being used) after thawing without suffering any harm. They recommended for use in the future only 1/10 L + mixtures, which experience so far had shown to be entirely safe. Their recommendation was adopted by the Massachusetts State Department of Health, and no further trouble was experienced.

Baden 1924

This incident was one in which a number of children became gravely ill, some of them fatally, as the result of being injected with diphtheria toxin in place of diphtheria toxin-antitoxin mixture.

In a home designed to house 100 infants, 18 to 20 nursing mothers, and 20 small children, an infant died of diphtheria on 8 September 1924. On the same day another infant became ill and, in spite of treatment with diphtheria antitoxin, it died three days later. On the 10th September, all the infants (28) and children (6) in the institute were schick-tested. Six reacted negatively. All of them, however, whether schick-positive or schick-

negative, were injected subcutaneously in the abdominal region on the 12th September with 1 ml of what is described as Löwenstein-Busson inoculation material—a mixture of diphtheria toxin and antitoxin (see Löwenstein 1930). Each dose came from a separate ampoule in a box of 50 received from the Vienna Serological Institute—a commercial manufacturing house.

That night and on the next day many of the injected children became restless. Swelling and redness appeared at the site of injection and spread during the following days up to the axillary and down to the inguinal region. Vesicles developed and subsequently skin necrosis. The affected children were given 2000 units of diphtheria antitoxin subcutaneously three days after the injection, i.e. on the 15th September. This, however, did not prevent four of the infants and three of the children over a year old from dying. The infants died within 4 to 9 days, the children not till the 12th, 17th, and 41st day. Post-mortem examination revealed haemorrhagic infiltration of the adrenals, with sometimes enlargement of the thymus, in all except the child that died after 41 days, who was found to have pachymeningitis, hydrocephalus, and acute pleurisy. In those that recovered, the skin manifestations began to abate about the end of a week, and the body weight to increase once again.

Of the 34 infants and children that were injected, 6 showed no reaction, 11 had quite mild reactions, and 17, of whom 7 died, had very severe reactions. In the first and second groups all of the children except two had received 500 units of diphtheria antitoxin on the 9th September, i.e. three days before the injection of the TAM. In only one of the children protected in this way did swelling of the skin, followed by necrosis, occur. It would appear that the two unprotected children who showed no reaction, both of whom were schick-positive, must have received an injection of some harmless material, as may possibly some of those who were given a protective dose of antitoxin. It may be noted that, whereas an injection of 500 units of antitoxin three days before the TAM injection afforded protection to all except one of the children, an injection of 2000 units three days after the TAM had no apparent effect.

EXAMINATION OF THE INJECTION FLUID

Altogether 146 ampoules from the same batch of TAM were collected from the children's home, from hospitals, institutes, and other places to which they had been sent, and examined by Professor R. Graszberger (1926) at the Hygienic Institute of the University of Vienna. Simple guinea-pig injection soon showed that they fell into two more or less equal groups—toxic and non-toxic. Quantitative investigations made it apparent that the ampoules in the toxic group all had the same degree of toxicity; and inquiries at the factory elicited the information that these had been filled on the 10th or the 21st July, whereas the non-toxic ampoules had been filled on other days. Further examination by precipitin and anaphylactic tests failed to reveal the presence of horse serum in any of the toxic ampoules, rendering it highly probable that they contained no antitoxin. At the factory it was found that flasks containing toxin and flasks containing toxin-antitoxin mixture were kept side by side in the same cold cabinet. The fluid in the toxic ampoules corresponded to a 1/10 dilution of the toxin in one of these flasks. As the MLD for a 250-gram guinea-pig of the toxin in this flask was contained in 0.01 ml, the injection material must have contained 1 MLD in 0.1 ml, so that the children given 1 ml must have received about 10 guinea-pig lethal doses. The evidence as a whole leaves little doubt that during the process of filling the ampoules a

toxin-containing flask had been used in mistake for one containing toxin-antitoxin mixture.

An alternative explanation put forward by Helmreich (1925) was that the ampoules had all been filled with TAM, but that in some of them dissociation had taken place with the liberation of pure toxin. This possibility was gone into very thoroughly by Professor Graszberger, who carried out numerous experiments on the effect of acid, of alkali, of phenol, of light, of freezing, and of simple storage on the combination of toxin and antitoxin without being successful in rendering the mixture more toxic by these means.

It may be concluded, therefore, that the toxic manifestations and deaths in the infants' home were due to the injection of diluted diphtheria toxin in place of toxin-antitoxin mixture, the toxic ampoules having been filled by mistake from a flask of toxin that was kept at the factory in the same refrigerator as flasks of TAM.

Tashkent 1926

The information about this incident is taken from an abstract of **a** paper by Jakovleva (1927) published in a Russian journal.

Fourteen children received by accident diphtheria toxin instead of anatoxin. Eight of them died within a fortnight and four more within a month after suffering from polyneuritis. The two remaining children suffered from general intoxication but eventually recovered.

The dose of toxin given to the children was about 100 units. It was administered subcutaneously. Though the mistake was quickly realized and 40 000 units of antitoxin were injected during the four following days, dysphagia became noticeable towards the end of the 5th week, followed by paralysis of the soft palate, legs, and diaphragm. Death occurred at about the 8th week.

It would appear that in some of the children, at any rate, the antitoxin prevented death from acute toxaemia but not from the later paralytic manifestations. It is difficult to be sure of this, however, since the history of only one of the children is given in the abstract.

Medellín, Colombia, 1930

Like the accident at Baden, the Medellín disaster resulted from the use of pure toxin in place of a harmless diphtheria prophylactic.

At the time, diphtheria was taking a heavy toll of life in Medellín as the following figures show:

Year	1928	105 cases with 45 deaths
	1929	109 cases with 68 deaths
	1930	271 cases with 30 deaths

It was therefore decided to introduce vaccination against the disease.

After preliminary schick-testing, 48 schick-positive subjects aged 1 to 8 years attending the Child Welfare Centre (las Salas Cunas) received in October 1930 a dose of 0.5 ml of anatoxin subcutaneously in what is described as the scapular region, but what was probably the arm near the shoulder. The anatoxin was prepared in a local laboratory. A second injection of 1 ml was given three weeks later; and a third of 1.5 ml of what was thought to be anatoxin but was in reality pure toxin, was given 15 days later, 14 November, at about 2 o'clock in the afternoon.

By the following day it was clear that something had gone wrong. A doctor was called in the early afternoon to a child who was gravely ill and who died a few hours later. Immediately a search was made for the other children that had been injected, and as many as could be found, fifteen in all, were given 8000 to 12 000 units of diphtheria antitoxin. That night three more children died after suffering from vomiting, diarrhoea, extreme restlessness, fever, a painful reaction at the site of injection, and later convulsions and coma. Before death the pulse was extremely rapid and almost imperceptible.

On the following day, 16 November, as the result of special appeals further children were located, taken into hospital and given serum treatment. The clinical symptoms and signs included early vomiting and diarrhoea, fever (102-104°F), rapid feeble pulse, intense dyspnoea, great restlessness, scanty micturition, a comatose or semi-comatose state, pallor and often cyanosis, generalized tonic convulsions, and a severe local reaction. In many of the children the tonsils were covered with a typical diphtheritic false membrane. Several of the children suffered from pain at the site of injection followed by widespread indurated oedema and ulceration.

Altogether 16 of the 48 children died, 14 within 24 to 60 hours of the third injection, i.e. on 15th and 16th November. One child died with special symptoms on 22 November; and the last child on 28 December, with paresis of the muscles of the head, neck and legs and dysphagia.

In the fully documented report of this incident by Ramirez (1931) clinical histories are given of all the children, but there is no call to reproduce these here. The symptoms varied according to the degree of immunity. One or two points, however, demand attention. In many of the children a false membrane was observed over the tonsils which disappeared on serum treatment. This observation is of particular interest, because it would appear as if diphtheria toxin had a special affinity for the pharyngeal mucosa, and that the local multiplication of diphtheria bacilli was not necessary for membrane formation provided toxin was present in the body. Ramirez considers other explanations, but as no diphtheria bacilli could be cultivated from any of the membranes and none of the patients was found to be a carrier of these organisms, he is forced to conclude that the toxin can be selectively absorbed by the mucous membrane of the throat—in much the same way as it is by the nerves and heart muscle.

Post-mortem examination of the children that died was not very illuminating. Microscopically there was slight congestion of the liver and the kidneys, intense congestion of the meninges over the cerebrum, cerebellum, and medulla, and the presence of an abundant white, protruding adherent false membrane in the pharynx. The adrenals appeared normal. Histologically, little attention can be paid to the findings, since the specimens were not taken till 32 hours after death, but various degrees of cellular lysis were observed in the liver, spleen, kidneys and adrenals.

Investigation showed that the fluid used for the third injection consisted of diphtheria toxin having at the time of injection an MLD for the guinea-pig of 0.004 ml. As the dose given to the children was 1.5 ml it follows that they must have received about 375 guinea-pig lethal doses.

It is regrettable that in the laboratory in which they were prepared containers of toxin and anatoxin were kept in the same refrigerator. Such conditions should never be permitted.

How much value did antitoxic serum treatment have when given 24 to 48 hours after the toxin? The author discusses this question at some length, and considers that, though it contributed to a favourable result, the children that recovered owed their life mainly to the active immunity they had developed as the result of their two previous injections of anatoxin. Had the serum been given intravenously, it might have been more effective, but in fact it was all given subcutaneously or intramuscularly. (For a slightly fuller account, see Report 1931.)

Italy 1933

The account of this incident is very incomplete. What is reproduced here is based largely on the paper by Frontali (1933) dealing with the clinical aspect only. So far as can be ascertained, no published report is available of the investigation set on foot by the Italian Government into the cause of the disaster.

In April 1933, several hundred infants and children in the provinces of Rovigo and Venezia became severely ill after injection with what was believed to be anatoxin. Over 30 of the children died. In the provinces of Milan, Varese, Genoa, and Treviso other children were affected but less severely and without fatal consequences.

The material used for injection was prepared by a private concern known as the National Serotherapeutic Institute of Naples. According to semi-official information at the time bottles of imperfectly detoxified material were sent out along with properly prepared anatoxin, but from the reactions that followed and from the number of deaths that occurred it is more reasonable to suppose that pure toxin was distributed by mistake. The director of the Institute, Professor Camillo Terni, and the technician responsible for preparing the anatoxin were arrested and taken into custody. Professor Terni died a year later as the result of an accident, and the whole incident was treated with the greatest official reticence.

CLINICAL PICTURE

After injection there was a local reaction consisting of redness 5-10 cm or more in diameter, and induration reaching a maximum in 48 hours. These were followed by a brownish pigmentation and scabbing, with ulceration exposing the deeper tissues and leading to permanent scar formation. The local reaction was accompanied by fever (102°-104°F) lasting for 2 to 5 days.

Then came a period of quiescence lasting for 3-6 weeks—shorter (20-25 days) in those injected in the mammary region and longer (40-45 days) in those injected in the gluteal region. After this latent phase a large proportion of children who were old enough to read lost partly or completely their power of ocular accommodation. Another common defect was convergent strabismus with occasionally unilateral or bilateral ptosis. The eye signs were accompanied as a rule by general asthenia and weakness of the lower limbs. In some cases definite paralysis was observed affecting the muscles of the neck, the back, and more rarely the diaphragm. Paralysis of the uvula and soft palate led to nasal intonation and a reflux of fluid through the nose during swallowing. Besides the more generalized effect of the toxin, monoplegia was noted in some cases, affecting the arm when the injection had been made in the mammary region and the leg when it had been made in the gluteal region.

Disturbances of sensibility were sometimes detectable, especially in the older children. They included paraesthesia, formication in the

extremities, and diminution in the muscular sense and the orientation of the limbs leading to ataxia. The patellar reflex was first exaggerated, then lost, and regained as recovery took place. One of the earliest symptoms was exaggeration of the oculo-cardiac reflex; in several hundred patients it was observed that compression of the eyeball led to stoppage of the heart.

Apart from the 30 or more children that died of diaphragmatic paralysis or myocardial degeneration, the affected children appear to have gradually got better, though there is no information on how long this took. Frontali discusses the mode of action of the toxin, and among other things concludes that pharyngeal paralysis is due to a specific selective effect of the toxin; local elaboration of toxin by diphtheria bacilli in the throat is unnecessary.

Kyoto, Japan, 1948

In this incident—the most serious of its kind—a toxic batch of alum-precipitated toxoid (APT) was responsible for illness in over 600 infants and children and for no fewer than 68 deaths. The following account is taken mainly from the paper by Kurokawa and Murata (1961), which differs in certain particulars from that by Barksdale, Garmise and Horibata (1960).

On 20 and 22 October 1948, a large number of babies and children in the city of Kyoto received their first injection of APT. On the 4th and 5th November, 15 561 babies and children aged some months to 13 years received their second dose. One to two days later 606 of those who had been injected fell ill. Of these, 9 died of acute diphtheritic paralysis in seven to fourteen days, and 59 of late paralysis, mainly in four to seven weeks. Of those that fell ill, about 80 per cent were in the first or second year of life, and of those that died over 90 per cent were in this age group. At the site of injection oedema, vesicle formation, necrosis followed by ulceration, and in relation to it axillary lymphadenopathy were seen. In addition, some children suffered from pharyngeal paralysis, paralysis of the diaphragm, suppression of urine, or heart failure.

Inquiry showed that only one of the four batches of APT used could be incriminated, and that only about half the vials of this batch were toxic. In the preparation of this batch the process of detoxification had been carried out in four bottles, the contents of which had then been filled separately without pooling into vials. No exact tests had been made on the toxicity of any of the four bottles. Titration in guinea-pigs revealed the presence of free toxin in about half the vials of the batch that had been responsible for illness. From the examination of numerous vials it appeared that the contents of two of the bottles had been imperfectly detoxicated.

There is an important discrepancy in the accounts given by Kurokawa and Murata on the one hand and by Barksdale and his colleagues on the other. According to Kurokawa and Murata the toxic vials contained 1/5 MLD per ml, whereas Barksdale and his colleagues estimate the amount as 10 MLD per ml. No explanation is available for so great a discrepancy. Though Kurokawa and Murata give detailed protocols of their findings, it seems probable that, as will be pointed out later (p. 41), the estimate of Barksdale and his colleagues is more likely to have been correct.

DISCUSSION

From these various experiences two points of interest merit brief discussion.

The fatal dose of diphtheria toxin for man

The first is the comparison of the fatal dose of diphtheria toxin for man with that for the guinea-pig. Information is available from six of the incidents considered here.

At Dallas children, 1-18 years of age, were injected with 1 ml of a toxin having an MLD for a guinea-pig of 250 g (½ 1b) of 0.1 ml. That is to say, the children received 10 MLD. Ten children died, seven of them within fourteen days. All the fatal cases were in the 1-5-year age group. The number of those injected is not known but was not less than 120.

At Baden 34 infants were injected with 1 ml of a toxin having an MLD for the guinea-pig of 0.1 ml. Like the children at Dallas, these infants each received about 10 MLD. Seven infants died, four of them within 4—9 days.

At Concord, 21 unimmunized children were injected with 1 ml of a toxin having an MLD for the guinea-pig of rather over 1 ml. Each child must therefore have received less than 1 MLD. All the children experienced severe local reactions, but none of them died.

In the Belgian incident of 1922, a single child was injected with 1 ml of toxin having an MLD for the guinea-pig of 0.01-0.008 ml. The child must therefore have received rather over 100 MLD. It died on the seventh day.

At Medellín 48 children aged 1-8 years were injected with

1.5 ml of a toxin having an MLD for the guinea-pig of 0.004 ml. That is to say, each child received about 375 MLD. Sixteen of these children died, 14 of them in 24-60 hours. It is probable that many more would have died, had they not been treated with antitoxin.

At Kyoto 606 babies and children aged some months to 13 years fell ill, and 68 died, after receiving 1 ml of imperfectly formolized APT containing what is stated to be 1/5 MLD by Kurokawa and Murata (1961) and 10 MLD by Barksdale, Garmise, and Horibata (1960). All these children had received their first dose of APT about two weeks previously, so that they probably had some slight degree of immunity to diphtheria at the time of their second injection.

The MLD is defined as the least amount of toxin that will, on the average, kill a guinea-pig of 250 g weight within 96 hours after subcutaneous injection. The lethal dose, therefore, is

2 MLD per lb of guinea-pig.

At Dallas 10 MLD proved fatal to some children weighing about 30 lb in 14 days. If they had died in four days, then the lethal dose per lb of child would have been 0.3 MLD, i.e. about one-seventh of that per lb of guinea-pig.

At Baden 10 MLD proved fatal to some infants weighing about 10 lb in 4-9 days. If they had died in 4 days, then the lethal dose per lb of child would have been 1 MLD, i.e. one-half of that per lb of guinea-pig.

At Concord rather less than 1 MLD failed to kill any of the children whose average weight was probably about 50 lb. That is, a dose of about 0.02 MLD per lb was not fatal.

In the Belgian incident of 1922 rather over 100 MLD proved fatal in 7 days to a child weighing about 70 lb. If it had died in 4 days, the lethal dose per lb of child would have been rather over 1.4 MLD.

At Medellín children of 1-8 years died in 24-60 hours, showing that they suffered from a more severe toxaemia than that caused by 1 MLD in a guinea-pig. What the minimal lethal dose was for these children cannot

be calculated. All that can be said is that a dose of 7.5 MLD per lb of child was more toxic for a child than 2 MLD per lb for a guinea-pig.

At Kyoto 9 infants and children died of acute diphtheritic paralysis in 7-14 days, and 59 of late paralysis mainly 4-7 weeks after their second injection. Over 90 per cent of the fatal cases were in children under three years of age. Though Kurokawa and Murata (1961) state that the toxic product contained only 1/5MLD per ml for a 250-gram guinea-pig, it is very difficult to believe this. Admittedly no deaths occurred within 4 days, but 66 out of 68 deaths occurred within 1 to 7 weeks.

This experience resembles that at Dallas and at Baden far more closely than at Concord and Bridgewater, suggesting that the APT at Kyoto must have contained a great deal more than \ MLD per ml. When it is further remembered that all the children at Kyoto had received a dose of APT a fortnight earlier and had therefore presumably some degree of immunity, it seems probable that the estimate of 10 MLD per ml given by Barksdale and his colleagues (1960) was more nearly correct.

Taking these six incidents together, it may be concluded that, weight for weight, there is little difference in the susceptibility of man and the guinea-pig to diphtheria toxin, but so far as the very limited information goes, it suggests that man may perhaps be slightly more susceptible. This conclusion is similar to that reached by Schmidt (1942), who took 12 MLD for a guinea-pig as being fatal for a child—presumably of 20 lb or so. On the basis that 1 MLD contains 0.0001 mg of toxin, Schmidt estimates that the fatal dose of toxin for a child is just under one-millionth of a gram.

Late toxaemia

The second point of interest is the occurrence of late toxaemia. Children who survive the acute toxaemic reaction may suffer some weeks afterwards from late paralyses. Schmidt (1942) notes that these are sometimes accompanied by renewed general toxaemia, as manifested by illness, vomiting, weakness, slight fever, cardiovascular impairment, asthenia, collapse, and sometimes sudden death. Schmidt regards 35-50 days as the common period for these happenings, and expresses the view that, if the child survives for 52 days, the danger of a fatal issue is past.

In many of the incidents recorded here late manifestations of toxaemia were evident. At Dallas late deaths occurred at 31, 39 and 46 days after injection, and some of the paralyses in surviving children did not come on till the 8th or 9th week. At Baden a late death occurred on the 41st day and at Medellín on the 44th day. In the Italian incident of 1933, after the acute toxaemic manifestations, there came a quiescent period followed 3-6 weeks after injection by paralyses affecting the eyes, skeletal muscles, the diaphragm, the heart, the uvula and the soft palate. Over 30 of the children died of diaphragmatic paralysis or myocardial degeneration. At Kyoto 59 of the 68 deaths occurred from late paralysis, mainly in 4 to 7 weeks.

It seems clear that toxin must remain in the tissues for a long time. It is also clear that, since late manifestations may occur in cases treated by antitoxin, the toxin is not destroyed by the antibody. The antitoxin probably disappears more rapidly than the toxin, leaving at times sufficient unaltered toxin to cause late manifestations of disease.

TETANUS TOXOID: FREE TOXIN IN THE VACCINE

Owing to technical errors in the preparation of tetanus toxoid, spores of the bacillus may survive and be incorporated in the vaccine. According to

Regamey (1965) this formerly resulted in the occurrence of numerous cases of tetanus after immunizing injections, particularly in Central Europe.

INHERENT INFECTIVITY

POLIOMYELITIS VACCINES

Inactivated vaccines

The earliest attempts at vaccination against poliomyelitis were made in the United States by Kolmer and his colleagues (Kolmer and Rule 1934a, *b,* Kolmer 1935, 1936) and by Brodie (1935) and Brodie and Park (1935, 1936).

Kolmer prepared his vaccines from the spinal cord of monkeys that had been infected intracerebrally with a remote passage virus. The cord was finely divided, treated with 1 per cent sodium ricinoleate, and left for 24 hours at 37°C and then for 14 days at 4-6 °C with daily shaking. Experiments showed that the virus was not completely destroyed, but that injected subcutaneously in repeated small doses into monkeys it protected them against a subsequent intracerebral inoculation of a live virus that killed all the control monkeys. This vaccine, consisting of a 4 per cent suspension of monkey cord in a 1 per cent solution of sodium ricinoleate, was used for the vaccination of 25 children, each of whom received 1-3 doses. No ill effects were noted. In 11 of the 25 children neutralizing antibodies appeared which had previously been absent, and in the remaining ten, in whom antibodies had been present before vaccination, the titre of the serum rose after vaccination. Later, Kolmer (1936) modified the preparation of the vaccine by treating the cord suspension with a 1 /80 000 solution of phenyl mercuric nitrate in addition to the 1 per cent sodium ricinoleate and keeping it for 10-14 days at 10-12°C. Large numbers of persons, mostly children under 15, were given three doses of this vaccine subcutaneously, and reports were received on 10 725 of them. Of these, ten suffered from poliomyelitis after the first or second dose.

Brodie and Park prepared their vaccine from monkey cord treated with 0.1 per cent formalin for 8-12 hours at 37°C (see also Nathanson and Langmuir 1963). Judged by intracerebral injection into monkeys, the virus appeared to be completely inactivated. Over 2300 persons received two 5 ml doses of this vaccine about 11 days apart. In practically every subject tested an antibody response was observed. Field trials were carried out with this vaccine and altogether more than 9000 persons were inoculated including children and nurses. Two cases of poliomyelitis were reported. Both had their onset 13 days after injection, and one of them proved fatal from bulbar paralysis.

Leake (1935), who inquired into the effect of these vaccines on behalf of the Public Health Service, reported that 12 cases of poliomyelitis had followed their use, of which 6 had proved fatal. Symptoms in these cases had come on 6-14 days after inoculation, and all the cases had occurred in circumstances that rendered natural infection improbable. Moreover, paralysis had affected first the limb into which the injection had been made or the contralateral limb. Leake concluded that further use of poliomyelitis virus for human inoculation was undesirable; and the Federal Government followed his advice and suppressed the vaccines. Thus ended ignominiously the first attempt—and a praiseworthy one it was—to confer artificial immunity against poliomyelitis.

Looking back, it is fairly clear that the failure in both vaccines to inactivate the virus completely was due to the presence in the cord suspension of particles too large to be effectively penetrated by the formaldehyde or sodium ricinoleate used as disinfecting agents. The necessity of ensuring the exposure of every particle of virus to the inactivating agent and of appreciating the limitations on the disinfecting power of formaldehyde in the presence of protein material was a lesson that was not learned till a similar catastrophe occurred many years later.

The Cutter incident

The outbreak of cases of poliomyelitis that followed the general introduction of the Salk type of inactivated poliovirus vaccine in April 1955 is generally referred to as the Cutter incident. The following account is compiled from various reports, principally Peterson, Benson and Graeber (1955), Report (1955a), Scheele (1955), Langmuir, Nathanson and Hall (1956), and Nathanson and Langmuir (1963). Many of the accounts were written up soon after the incident had occurred, before the full extent of the damage was known. I have therefore relied mainly for the figures on those given by Nathanson and Langmuir (1963) in their retrospective survey seven to eight years later.

The successful cultivation of the poliovirus in monkey kidney cells by Enders, Weller and Robbins (1949) opened the way for the preparation of a vaccine grown in non-nervous tissue outside the body. A formolized vaccine containing the three types of poliovirus was introduced by Salk (1953; see also Salk *et al.,* 1954, 1955), and was submitted to a field trial in the United States in 1954. The results, as analysed and reported on by Francis and his colleagues (1955, 1957), and by Francis (1957), were favourable, and publication of the summary report on 12 April 1955 was followed by the release of vaccine prepared by five different manufacturers—Parke Davis, Eli Lilly, Cutter, Wyeth and Pittman Moore. During the next few weeks over five million subjects were inoculated. On 26 April six cases of poliomyelitis were recognized among children who had received the Cutter vaccine. This vaccine was at once recalled, but further cases continued to occur, together with a few after the Wyeth vaccine.

Following the primary cases of inoculation poliomyelitis came secondary cases among family and community contacts. Altogether there were 260 cases of poliomyelitis constituted as follows:

94 cases in vaccinated persons, of which 59 were paralytic.
126 cases in family contacts, of which 101 were paralytic.
40 cases in community contacts, of which 32 were paralytic.

Ten deaths occurred, five in the vaccinated and five in the contacts. Of eight batches of vaccine prepared by Cutter's, only two were incriminated. These had been used, principally in California and Idaho, to inoculate 120 000 subjects, thus giving an attack rate of 94 in 120 000 or about 1 in 1300, or a paralytic attack rate of 59 in 120 000 or about 1 in 2000. The incubation period of the cases was 3-25 days after injection, mostly 5-9 days, with a median of 8 days. The shortness of this period was ascribed to the use of the highly virulent type 1 Mahoney strain in the vaccine and the intramuscular route of injection. Unlike the natural disease, the arms were affected twice as often as the legs; and the left arm, into which injections are commonly made, was affected more often than the right. In contacts

the median incubation period was 24 days—longer than would be expected from a double incubation period.

Poliovirus was isolated from about 80 per cent of the inoculated children examined and from 15 per cent of household contacts. Most of the strains belonged to type 1. This type was actually recovered by Gebhardt and Bachtold (1956) from one of the suspected batches of Cutter vaccine, and by Eklund, Bell and Hadlow (1956) from two of the batches using monkey inoculation; Eklund also recovered type 3 virus from one of the batches by tissue-culture methods (see Peterson *et al.* 1955). It may be remarked that the isolation of poliovirus when present in vaccinal material in only very small amount is not easy. Monkeys can, however, be rendered more susceptible by pre-treatment with whole-body X irradiation and subcutaneous injection of cortisone (Syverton, Brunner, Tobin and Cohen 1956).

Inquiry showed that in the preparation of the vaccine the virus in some lots had not been inactivated by treatment with formalin. These were treated a second, and some a third time, not always successfully (Scheele 1955). Investigation by various workers (Timm *et al.* 1956, Haas *et al.* 1957, Wesslén *et al.* 1957) revealed the limitations of formaldehyde as a disinfectant in the presence of protein. This was largely a rediscovery of what was already known but had been overlooked or forgotten. Disinfection by formalin does not conform to a first-order reaction, and is affected by so many factors that it is extremely difficult to foretell the end-point with any degree of accuracy.

Veldee (1955), who gives a good account of the limitations of formaldehyde, doubts whether a vaccine inactivated by this substance can ever be guaranteed to be safe. The virus in the suspension may be partly clumped, and may be surrounded by gelatinous debris of protein material. This is hardened by the formaldehyde, so that the virus particles within are protected from its action. Inside the body, the coating is digested by enzymes and the virus particles are set free. The concentration of formaldehyde on each virus particle varies not only with the number and degree of aggregation of the particles, but with the relative affinity for the various components of the virus suspension, such as amino acids, traces of protein from the monkey kidney tissue cells, and probably other substances. Thus the different steps in the procedure of inactivation are accompanied by unpredictable variables. The manufacturer is faced with the alternatives of using too much formalin and risking the immunizing potency of the vaccine, or using too little and risking the survival of a few virus particles. The final concentration selected must necessarily be something in the nature of a compromise. So long, however, as the suspension is adequately treated to remove aggregations of virus particles and unnecessary extraneous material, the safety of the product can be reasonably assured. The risk taken by a manufacturer can be gauged from the fact that 60 lawsuits were brought against the Cutter laboratory, and that 54 of these had been settled by April 1962 for a total of over 3 million dollars.

Cases of poliomyelitis in children inoculated with Salk vaccine, coming on within 3-4 weeks of injection, have continued to occur, even since steps were taken to improve the manufacturing process and tighten up the methods of control (Geffen and Spicer 1960).

Roden (1964) would regard the most significant kinds of association between injection and paralysis as: (1) an unduly high incidence of poliomyelitis in vaccinated persons; (2) an aggregation of dates of onset of illness within a month of vaccination, particularly 4 to 14 days; (3) an

undue proportion of persons paralysed in the inoculated limb; and (4) an undue proportion of cases associated with a single batch, or a small number of batches, of vaccine. Even with these criteria, however, it has proved impossible to decide whether the cases reviewed by Geffen and Spicer (1960) and by Geffen (1960) were cases of inoculation paralysis or cases occurring by chance in children who happened to have been recently inoculated.

Reports, summarized by Roden (1964), showed that, apart from poliomyelitis, there were 27 cases of neurological illness between 1956 and 1963 among a total of over 12 million persons receiving Salk vaccination. Among these were five cases of ataxia, including two of disseminated sclerosis, coming on within three weeks of a first injection; one case of disseminated sclerosis with onset six weeks after a second injection; and three cases of ataxia occurring within four weeks of a third injection. This clustering of cases might suggest a relation between Salk vaccination and nervous illness; but, as Roden points out, among a total of over 12 million vaccinated persons it is probable that at least 60 cases of disseminated sclerosis would have been expected within a year of the first injection without any aetiological relation to the vaccine. In fact, only three such cases were reported, suggesting strongly that their occurrence was merely coincidental.

So many million doses of Salk vaccine have now been given with such beneficial effects and with so relatively few questionable accidents that it is generally regarded as sufficiently free from danger to justify its general use.

One curious feature of the Cutter incident was the high proportion of family and community contacts that suffered from poliomyelitis. In natural outbreaks of this disease multiple paralytic cases are uncommon and, when they do occur, are often more or less simultaneous (Aycock 1941, Littell and Smith 1955, Spicer and McDonald 1957). Yet in the Cutter incident far more cases of paralytic poliomyelitis occurred among the contacts than among the vaccinated children themselves. The explanation for this is by no means clear.

Live attenuated vaccines

The use of live attenuated strains of poliovirus to be given as a vaccine by the mouth we owe primarily to Koprowski and his colleagues (Koprowski, Jervis and Norton 1952, 1954, Koprowski 1955). It was Koprowski who adapted strains of the different types to mice by repeated intracerebral passage and in so doing modified their virulence. The resulting strains were found to be so far attenuated as not to give rise to poliomyelitis on intracerebral injection into monkeys, and only seldom on intraspinal injection. Later, further strains were attenuated by Cox at the Lederle laboratories, and by Sabin in Cincinnati. For the purpose of reference the three sets of strains are:

	Type 1	Type 2	Type 3
Koprowski group	Wistar-Chat	TN or P 712	Wistar Fox
Lederle-Cox group	Lederle-SM	Lederle MF	Lederle Fox
Sabin group	L.Sc. 2 ab	P 712, Ch 2 ab	Leon, 12 ab.

The two P 712 strains are identical, as are also the two Fox strains.

Cox (1954), like Koprowski, used rodent-adapted strains, but Sabin (1957a, *b,* 1959) and Sabin, Hennessen and Winsser (1954) went further

and made their final selection by the terminal dilution or plaque purification of attenuated strains grown in cultures of monkey kidney tissue.

Vaccines prepared from these strains quickly came into use in many different countries. The Koprowski vaccine was used on a large scale in the Belgian Congo and in Poland; the Lederle-Cox vaccine in Florida, Nicaragua, Colombia, Uruguay and Costa Rica; and the Sabin vaccine in Mexico, the USSR and other countries of Eastern Europe, in Singapore, Vietnam, China and South Africa. In view of the Cutter incident the United States in general and Great Britain in particular were cautious in embarking on the use of a new vaccine composed of strains whose fixity and innocuousness for man were still in doubt. Numerous investigations were made, and at the two international congresses held at Washington in 1959 and 1960 (Report 1959*b*, 1960*a*), all the evidence both from the laboratory and the field was reviewed. It was shown that on passage through the intestinal canal of man the strains might undergo a change and become more virulent for monkeys (Melnick, Benyesh-Melnick, and Brennan 1959), but no evidence was produced to prove that this increase in virulence was progressive. (See also Sabin 1965.)

In spite of the enormous scale on which the live vaccines had been used—the USSR alone had issued over 100 million doses by early in i960—no ill effects had been traced to them and no case of poliomyelitis had been attributed to them. The Expert Committee of the World Health Organization (Report 1960*b)* reported in favour of using type 1 and type 2 strains of the Sabin set, but was a little doubtful about the safety of type 3. Henceforward the Sabin vaccine came to be progressively adopted throughout the world, and in the United States and in Great Britain thorough surveillance programmes ensured that any cases of poliomyelitis associated with the vaccine would be thoroughly investigated.

So far, serious suspicion has been cast on the use of live attenuated vaccines on only two occasions, one in Germany in i960, and one in North America between 1962 and 1964.

The West Berlin incident, 1960

According to Raettig (1962), from whom this account is taken, 280 000 persons in West Berlin received a single oral dose of the Lederle-Cox live attenuated vaccine between the nth and 20th May 1960. The dose of 2 ml contained $10^{6.5}$ plaque-forming virus units of each type. The 280 000 persons were made up of 54 000 pre-school children, 193 000 school children, and 33 000 adults. Subsequent to the vaccination 48 cases of poliomyelitis were reported in West Berlin during the remainder of the year, of which 25 occurred within four weeks of the vaccination.

Raettig analyses these figures and comes to the conclusion that many of the cases were attributable, directly or indirectly, to the vaccine. His reasons are mainly (a) that most of the cases occurred at a time of the year—May and June—two to three months earlier than the usual seasonal epidemic; (b) that the cases were randomly distributed over the whole of West Berlin and not aggregated into groups as they so often are in a natural outbreak; (c) that two-thirds of the cases were in adults; (d) and that, of the 25 cases occurring in the 4-week period following vaccination, 17 had received the vaccine, giving an attack rate fifteen times higher among the vaccinated than among the unvaccinated population. Of the eight unvaccinated cases, it may be remarked, six had been in contact with vaccinated persons.

Raettig has no doubt on the responsibility of the vaccine for the cases that were closely associated with it in time, but he does not believe that the action was a direct one. If it had been, he thinks far more cases would have occurred. He is of the opinion rather that the vaccine acted by provocation, stimulating the natural wild virus to invade the blood stream and the central nervous system and thus give rise to disease (see provocation poliomyelitis, p. 270). His argument is not convincing.

In the first place there is no reason why an attenuated strain should not possess just enough virulence, and no more, to cause illness in a few highly susceptible members of the community. The balance between the virulence of an invading parasite and the resistance of the host is one that ranges from 0 to 100 per cent. Occasionally the organism may be so virulent as to attack practically the whole population—as with measles among a virgin community—or it may be so low as to cause no more than a latent infection without clinical illness—as with *Haemobartonella muris* in rats or the encephalomyelitis virus in mice. That only a very small proportion of the vaccinated population in Berlin suffered from poliomyelitis is therefore no argument against a direct effect of the vaccinal virus.

In the second place, though the occurrence of provocation disease is well recognized after the subcutaneous or intramuscular injection of various vaccines, there appears to be no similar record after oral vaccination. Indeed, it is not easy to understand what mechanism could operate after oral vaccination to facilitate the passage of a latent wild virus in the intestine to the central nervous system. The injection of a vaccine into the tissues may, by its irritant effect, enable an organism circulating in the blood to settle down locally and multiply before again invading the blood stream, or, as with the virus of poliomyelitis, passing through the nerve endings and nerves up to the spinal cord. Alternatively, it may have a reflex action rendering the blood vessels in the spinal cord in the part corresponding to the site of injection more permeable, thus allowing the virus to penetrate the nervous system. But what action could a virus administered by the mouth have on a wild virus in the intestine? It could hardly stimulate it to cause a viraemia. More probably, it would enter into competition with it, inhibit its growth, and possibly even lead to its elimination, in much the same way as other enteroviruses are known to do. The different effect of enteral and parenteral administration of a vaccine is well recognized in practice, when oral vaccination is given to combat an established outbreak of poliomyelitis under conditions in which the injection into the tissues of a killed vaccine would be fraught with the risk of provoking latent infections into activity.

Whatever the explanation, however, there seems little doubt that the incident in West Berlin in 1960 was associated with the administration of the Lederle-Cox vaccine.

North America 1962-4

Between 1961, when oral poliomyelitis vaccine was first made available for general use in the United States, and May 1964 about 100 million doses of each of Sabin's three poliovirus types of vaccine were distributed, and many more million doses of the trivalent vaccine. In 1962 small groups of poliomyelitis cases were reported in California, Nebraska and North Carolina, occurring among vaccinated persons living in a non-epidemic area. Four cases also occurred in Canada, all caused by type 3 virus, among four million vaccinated persons. Further cases followed in

the United States, and the Surgeon General of the Public Health Service set up a special advisory committee to determine how far they could be attributed to the vaccine. The committee met at the Communicable Disease Center at Atlanta on the 17-18th July 1964 and reviewed all cases reported since oral vaccines became available (Report 1964c). In non-epidemic areas 87 such cases were on record, of which 57 were regarded by the committee as being 'compatible', that is, as possibly due to the vaccine. The criteria of 'compatibility' were: (a) an onset of illness between 4 and 30 days after vaccination ; (b) significant residual lower motor neuron paralysis; (c) laboratory findings not inconsistent with multiplication of the vaccinal strains; (d) no evidence of upper motor neuron disease, definite sensory loss, or progression or recurrence of paralysis one month or more after the onset.

Of the 57 compatible cases, fifteen followed type 1 vaccine, two type 2, thirty-six type 3, and four the trivalent vaccine. Three-quarters of the cases were in adults, forty-four being 15 years of age or older. Most of the cases were widely scattered, occurring in 49 counties in 24 states, and in most the onset was between 8 and 21 days after vaccination. Admitting that it was not possible to prove that any individual case was caused by the vaccine and that no laboratory tests available could distinguish with certainty between a vaccinal and a wild strain, the committee nevertheless concluded on epidemiological evidence that at least some of the 57 cases were caused by the vaccine. The extent of the risk they estimated for the different virus types as:

Type 1	One case in 6 million doses
Type 2	One case in 50 million doses
Type 3	One case in 2 .5 million doses

They regarded type 3 vaccinal virus as being accompanied by more risk than the other two types, and unimmunized adults in rural areas or among the upper socio-economic groups as being the most vulnerable members of the community.

Many of the conclusions of the committee were criticized by Sabin (1964) both on factual and on theoretical grounds. In his opinion difficulties in clinical diagnosis, failure to demonstrate a rise in antibodies to the suspected strain, failure to disprove the causative role of other enteroviruses, and various statistical assumptions rendered doubtful some of the committee's conclusions, particularly the estimates of the incidence of poliomyelitis after the different vaccinal types. Sabin, however, agreed with the committee that, if any risk did exist, it was very small, and should not be allowed to interfere with the practice of routine immunization of all infants followed by a reinforcing dose to children on entry to elementary school.

Interpretation of the committee's findings is very difficult and it is impossible to be certain how many of the genuine cases of poliomyelitis were really caused by the vaccine. Coincidence alone may well explain some of them. In this connection it may be pointed out that both in the United States and in Great Britain numerous cases of paralysis have occurred within 4 weeks of inoculation with apparently satisfactory batches of Salk vaccine. The British figures collected by Geffen and Spicer (1960) have already been quoted (p. 47). The American figures for 1959-61 are given by Sabin (1963).

In 1959 68 million doses of Salk vaccine were shipped and 259 cases of paralytic poliomyelitis were reported within 30 days of its use.

In 1960 the corresponding figures were 52 million doses and 116 cases.

In 1961 the corresponding figures were 42 million doses and 26 cases.

The occurrence of these cases was just as impressive as those after the Sabin vaccine. They may have been due to the failure of a few particles of virus to be inactivated by the formaldehyde during processing of the vaccine, but they have been generally regarded as coincidental. If the Sabin vaccine is to be incriminated on epidemiological grounds, then so also must the Salk.

It may be noted that paralytic disease simulating poliomyelitis can be caused by the mumps, herpes simplex, Coxsackie A 4 and A 7, echo, and Russian spring-summer encephalitis viruses (Gelfand 1963).

BRITISH SURVEILLANCE OF THE SABIN VACCINE

In Great Britain the Sabin vaccine came into general use in February 1962. From then till the end of 1964 about 18 million doses of the trivalent vaccine were administered in England and Wales. An intensive surveillance programme was carried out by the Epidemiological Research Laboratory of the Public Health Laboratory Service designed to learn of every case of poliomyelitis diagnosed in the country (Miller and Galbraith 1965). During 1962-4 a total of 331 confirmed cases—278 paralytic and 53 non-paralytic—were reported. Among these were 20 paralytic patients who had received oral vaccine within the 28 days preceding the onset of illness. In seven of these the symptoms came on within 5 days of vaccination; six of these seven were vaccinated during the course of an epidemic in Monmouthshire and were almost certainly infected at the time of vaccination. Of the remaining thirteen cases, seven made a complete or almost complete recovery and in two the diagnosis was doubtful. There were therefore only four cases, three of them in infants, occurring 16-19 days after vaccination, in which there was residual paralysis. This represents an incidence of one case in every 4½ million doses given.

Apart from the chronological association with vaccination there was no evidence to suggest that the vaccine was aetiologically responsible for these cases. Sixteen batches of vaccine prepared by three different manufacturers had been distributed, and there was no special relation of the disease to any one of them. The proportion of all confirmed paralytic cases of poliomyelitis that were associated with the vaccine in each year changed little despite variations in the amount of vaccine used. Studies of the history, age, sex, and seasonal and geographical distribution of the cases revealed no striking or unexpected differences between vaccine-associated and other cases. Little help was gained from a study of the viruses isolated, because of the practical impossibility of distinguishing between vaccinal and wild strains. The fact that type 3 virus was isolated rather more often than type 1 or type 2 was explicable on the basis of previous observations that type 3 virus is excreted for a longer time after oral administration than the other two viruses (Report 1962*b*).

The only reasonable conclusion to be drawn from the English and the American figures is that, if the Sabin vaccine does give rise to poliomyelitis—and this is doubtful—it does so on such rare occasions as for all practical purposes to be negligible. No other vaccine used in the whole range of human medicine can claim a greater degree of safety. Had other vaccines been submitted to the same intensive scrutiny as the Sabin vaccine has received it is probable that the sorry record of disasters and mishaps that I relate in these lectures would have been very much longer than it is.

Only two more subjects of minor importance need be touched on in relation to poliomyelitis vaccine.

Facial paralysis in West Germany

Bodechtel and his colleagues (1963) reported that, after the administration of Sabin's oral vaccine to 22 million persons in West Germany, 52 cases of illness were reported that appeared to be associated with vaccination. In 21 of these the symptoms resembled those of poliomyelitis; they came on 3-82 days after vaccination, mainly 5-15 days. In 31 of the 52 cases the symptoms were those of facial paralysis, polyradiculoneuritis, or encephalitis. Poliovirus type 1 was isolated from four of these patients and Coxsackie virus from one. Whatever the explanation of these cases may be, it seems very doubtful whether they were in any way causally associated with the vaccine.

Vacuolating agents in poliomyelitis vaccine

Rhesus monkeys are subject to natural infection with a number of different viruses referred to as simian viruses. Some of these make their presence noticeable in cultures of monkey kidney cells. One of them, SV40, may be found in both the Salk and the Sabin vaccine unless measures are taken to prepare cultures only from uninfected monkeys. It is rather more resistant to formaldehyde than the poliovirus and may therefore persist, though in diminished quantity, in Salk vaccine. In Sabin vaccine it was reported by Sweet and Hilleman (1960) to be present in the order of about 10 000 particles per ml or rather more. Antibodies may be formed in response to the virus in Salk vaccine, much less often, if at all, in Sabin vaccine (Goffe, Hale and Gardner 1961). Though its presence is undesirable, there is no evidence as yet to show that it is harmful to human beings.

MENINGO-ENCEPHALITIS AFTER YELLOW FEVER VACCINE

Yellow fever vaccine is a live vaccine prepared from a strain of virus that has been attenuated by mouse or egg passage.

The original vaccine of Laigret (Sellards and Laigret 1932) was made from a strain of virus that had been adapted to white mice by Theiler (1930) and passed repeatedly through the mouse's brain. During the process it had lost its ability to produce the visceral lesions of yellow fever, but had acquired the power of causing encephalitis in mice and monkeys inoculated intracerebrally. For human use the vaccine was injected subcutaneously.

This strain was modified by Peltier (1946), who continued its passage through the mouse brain. A vaccine, generally referred to as the Dakar vaccine, was made from the 256th to 258th passage. Paralysed mice were killed on the 4th or 5th day and their brains, after storage at – 25°C for 6 days, were ground up and freeze-dried. For use, the dried vaccine was suspended in gum arabic solution and inoculated on to the arm by scarification (see Durieux 1956). Both these vaccines have been used chiefly by the French in Equatorial and West Africa.

The British and Americans, on the other hand, have used a vaccine made from the so-called 17 D strain. This was developed by American workers (Theiler and Smith 1937), who grew the original virus—the highly virulent pantropic Asibi strain—in tissue culture first of mouse embryo, then of whole chick embryo, and finally of chick embryo from which the brain and cord had been removed. The resulting strain was

avirulent for monkeys, but produced fatal encephalitis in mice after an incubation period of 8 days. The virus is propagated in eggs, and for use the vaccine is injected subcutaneously.

The first reports of encephalomyelitis were made by Lhermitte and Fribourg-Blanc (1936) and Darré and Mollaret (1936) after the use of Laigret's vaccine. In Lhermitte and Fribourg-Blanc's case a man of 52 years experienced a severe reaction characterized by fever, occipital headache, and vertigo, followed in a few days by sensory disturbances and partial loss of power in the lower limbs. After an intermission of three months, the trouble returned and passed gradually into an amyotrophy of the lower limbs and paraplegia. Later came bulbar symptoms, convulsive movements of the legs and diaphragmatic spasms. The patient died after 18 months. At post-mortem sub-acute myelitis was found; histologically the axis cylinders were intact but there was some demyelination; there were also degenerative lesions in the brain. Whether these lesions were the direct result of the vaccine or were those of multiple sclerosis, as is suggested by Barraux, Montel and Bordes (1936), it is impossible to say. In Darré and Mollaret's case a woman of 25 years suffered from high fever, headache and general convulsions eleven days after an injection of the vaccine. Meningeal symptoms appeared together with narcolepsy and mental confusion. Gradual recovery, interrupted by relapses, occurred over a period of two months. Mollaret and Findlay (1936) state that the batch of vaccine used for this injection gave rise to nervous disturbance in at least three other persons who were injected with it.

According to Stuart (1956) occasional cases of nervous disturbance followed the use of the Dakar vaccine in French West Africa, but in the Brazzaville area of French Equatorial Africa 102 cases of meningo-encephalitis with 18 deaths occurred among 102 000 persons vaccinated by scarification with a combined yellow fever and smallpox vaccine during September 1944. In 1951 there were 12 cases of encephalitis in children with 3 deaths after the use of the Dakar vaccine in Costa Rica; and in 1951-2 there were 83 cases, mostly in children, with 32 deaths among 142 000 inoculated persons in Nigeria. Other cases occurring singly or in groups are referred to in Stuart's (1956) review.

Trouble was also experienced with the 17 D strain. In the Guanhães area of Brazil in 1941 seven lots of vaccine were used for immunizing 55 073 persons. Encephalitis occurred in 199 (0.36 per cent) of these subjects after an average incubation period of 12.7 days. Only one case proved fatal, but convalescence in the others was usually protracted, and two children were left with brachial neuritis, an uncoordinated gait and mental retardation. The symptoms consisted of high fever, violent headache, nuchal pain and rigidity, somnolence proceeding particularly in children to torpor, nausea, vomiting sometimes continuing for days, delirium, and less often giddiness, photophobia, hyperexcitability and convulsions. The Kernig sign was positive and there was an excess of lymphocytes in the spinal fluid. These findings pointed to the existence of a meningo-encephalitis. Besides the cases diagnosed as encephalitis there were 83 patients who suffered from a severe reaction, consisting of fever, intense headache, anorexia, nausea, vomiting and somnolence. They were ill for five days or longer or were confined to bed for two days or more. The borderline between these cases and those in the former group was not easy to draw.

After this, four new sub-strains, apparently free from encephalitogenic properties, were used for the preparation of fresh vaccine. The new vaccine was tested in Brazil along with one lot of the old vaccine. Among

9870 persons injected with the new vaccine there were 6 cases (0.06 per cent) of encephalitis, and among 2973 persons injected with the old vaccine there were 49 cases (1.65 per cent). This comparison left no doubt in the minds of the observers (Fox, Lennette, Manso and Aguiar 1942) that the vaccine itself, and not any extrinsic agent, was responsible for the encephalitis.

Henceforward 17 D vaccine was standardized according to the 'seed lot system', by which only primary or secondary subcultures from the freeze-dried strain were used. This proved successful for the vaccination of adults, but occasional cases of encephalitis occurred in infants. Altogether fourteen of these had been reported by 1956 (Stuart 1956). It seems clear that the use of yellow fever vaccine should be avoided, when possible, during the first year of life.

Though there is very little information on the post-mortem findings in the fatal cases of encephalitis, there is fairly strong evidence for believing that these resulted from an invasion of the nervous system by the yellow fever virus. Macnamara (1953) actually demonstrated the virus in the brain of three out of four patients that had died of encephalitis after vaccination with the French neurotropic virus. If this interpretation is correct, it follows that the meningo-encephalitis occurring after yellow fever vaccine is of an entirely different nature to the encephalomyelitis which occasionally follows vaccination against smallpox or rabies (see pp. 157, 180).

VENEZUELAN EQUINE ENCEPHALOMYELITIS VACCINE

Sutton and Brooke (1954) reported that 14 out of 327 persons given a total of 1174 injections of a formolized vaccine containing the Venezuelan equine encephalomyelitis virus suffered from an acute febrile illness 3-6 days after inoculation. The illness had an abrupt onset and was characterized by constitutional disturbance without localization. The prominent symptoms were fever, rigors, severe headache, with often general muscular pain, lethargy, prostration, and visual blurring, and sometimes nausea, vomiting and diarrhoea. Most of the patients were well again in a few days; none died. Virus was recovered from the blood of seven out of eight patients examined and from throat washings in five patients. Neutralizing antibodies reached a diagnostic level within 2-3 weeks and usually attained a concentration of 1/1 000 000 or so. Most patients became ill after the first or second dose of vaccine, but one man did not go down till the third dose given 6 weeks after the first.

The vaccine was prepared from chick embryos infected with a strain of Venezuelan encephalitis virus isolated in Trinidad. The crude suspension was treated with 0.2 per cent formaldehyde *(sic)* and kept for three days at 21.5°C before being finally purified. It satisfied the requirements of the National Institutes of Health for sterility and non-infectivity. Later, when suspicion was thrown on it, the formaldehyde concentration was increased to 0.425 per cent; even this, however, did not sterilize the vaccine.

In a special investigation 6000 animals of various species were injected with concentrated vaccine, but in no instance was any virus recovered. This suggests that man is more susceptible to the virus than any of the laboratory animals, and shows how difficult it is with a new product to be sure that it will be inoffensive for human use (see Smith, Mamay, Marshall and Wagner 1956).

MEASLES VACCINE

So far as is known, only one death has been recorded after the use of live measles vaccine. That was in a child suffering from leukaemia who died from giant cell pneumonia. Death was apparently accelerated by the vaccine (Report 1966).

VIRULENT RABIES VIRUS IN THE VACCINE

Post-vaccinal or laboratory rabies

Before describing the encephalomyelitis that is not infrequently seen as a complication of antirabic vaccination (p. 180), it is necessary to refer to the occurrence of true rabies in the patient resulting from the presence in the vaccine of living virus. Several cases of this sort are on record. Busson (1926) reviewed eight fatal cases in which virus fixe was demonstrated by animal inoculation in the central nervous system of the patient at autopsy. He himself reports three cases. In one of these the patient died of myelitis starting 16 days after the end of treatment with Pasteur's dried cord vaccine. The other two, in which rabies in the biting animal was excluded, were treated by Högyes' vaccine; neurological symptoms came on 20-23 days after the last dose of vaccine and virus fixe was demonstrated in the central nervous system by animal inoculation. In these three cases the symptoms were partly those of rabies and partly those of myelitis. Herrmann (1926) showed that the virulence of the virus fixe was not in fact fixed and that subcutaneous injection into animals might cause death from rabies. He stated that some persons who had never come into contact with the street virus had suffered from rabies after vaccination and that rabies virus had been demonstrated in their saliva, blood, cerebrospinal fluid or brain by inoculation into animals. According to Remlinger (1952), thirty cases of paralysis after vaccination had been clearly shown to be caused by virus fixe. The danger is greatest with Högyes' vaccine—an opinion in which Busson (1926), Herrmann (1926) and Remlinger (1952) all concur. The number of virus particles increases progressively with rabbit passage, and simple dilution of the cord suspension, as in Högyes' method, may lead to the injection of too large a dose of living virus to be dealt with by the patient (Schweinburg 1930, Remlinger 1952).

Accidents may, however, follow the use of so-called killed vaccine owing to inadequate processing. A very serious occurrence of this sort occurred at Fortaleza, Ceará, Brazil, in i960. No fewer than 18 out of 66 persons vaccinated with Fermi's carbolized vaccine suffered from encephalomyelitis, and every one of the eighteen died. The vaccine, which was a suspension of sheep brain treated with 0.5 per cent phenol, had not been tested properly by the manufacturing laboratory either for potency or for innocuity. It was injected in 2 ml doses daily or on alternate days. Symptoms came on 4-13 days after the beginning of treatment, and the illness proved fatal in 2-9 days, usually 5 days. It was characterized by general malaise, myalgia, pain in the neck, continuous high fever, intense headache, muscular spasms, convulsions, dysphagia, diplopia, and frequent projectile vomiting, followed by paralyses, intense dyspnoea, abundant salivation, urinary incontinence, torpor, coma and death. Post-mortem examination of the central nervous system was made in three cases. The histological picture was that of perivascular infiltration, chromatolysis, neuronolysis and neuronophagia in the cerebrum; a lymphocytic inflammatory reaction in the cerebellum affecting the cells of Purkinje, some of which showed degeneration; and degenerative-inflammatory lesions of panmyelitis in the medulla. No Negri corpuscles were found. Injection of material into several species of animal led in

nearly all the animals to death from paralytic rabies. Fixed virus was also demonstrated in the vaccine itself in large amounts; the LD 50 for the mouse was 10^{-5} to10^{-7}. The patients undoubtedly died from infection with fixed virus. Presumably the very short incubation period was due to the high concentration of live virus in the vaccine; it was demonstrable in a 1/1000 dilution (Pará, Passos and Filho 1964).

One question must be asked. Is the finding of the rabies virus in the brain sufficient proof that the patient's illness was caused by the virus, or may the fixed virus be found in the brain of a vaccinated patient who has died from some other cause? Remlinger (1927*a*) discusses this question at some length. After the injection of a vaccine containing live virus it would not be altogether surprising if some of this should find its way to the central nervous system; and indeed the finding of *fixed virus* was reported by Quast (1925-6) in the brain of a vaccinated patient who died of tuberculous meningitis. Attempts by various workers to repeat such a finding in animals have failed. Nor have attempts to demonstrate *street virus* in the brain of symptomless animals injected some time before with this virus been any more successful. Such attempts were necessary after Paltauf (1909) claimed to have found street virus in the brain of patients who had been bitten by a rabid animal, had been vaccinated, and had died during the course of treatment or afterwards from some disease, such as arteriosclerosis, pulmonary embolism or delirium tremens, that had nothing to do with rabies. Remlinger concludes that, except in the rarest cases, the *street virus* is never found in the brain of a healthy patient unless he is in the incubation period of rabies; nor is the *fixed virus* found in the brain of a healthy patient except as the result of treatment with an unsatisfactory vaccine. The finding of either virus shows that the patient had succumbed to rabies—either of the street or the laboratory variety—or was in the incubation period of the disease.

Without questioning Remlinger's conclusion, it must however be pointed out that the incubation period of rabies may be very long—occasionally as long as a year (Bassoe and Grinker 1929) or even 17 months (Busson 1926)—so that it might happen that the virus was found in the brain of a patient who had died from some other cause during the incubation period of rabies. But, as Remlinger implies, such cases must be rare. It may be too that, as in Quast's case, meningeal inflammation permits access of the virus to the brain.

5

FAULTY PRODUCTION: FOREIGN TOXIN PRESENT

THE PRESENCE of a foreign toxin not caused by bacterial contamination during the preparation, storage, distribution or administration of the vaccine or antiserum must be very uncommon. Indeed the following incident is the only one of its kind of which I have found a record in the literature.

St Louis, Mo., 1901

In this incident tetanus followed the injection of diphtheria antiserum, not because the serum was contaminated with tetanus bacilli, as in the Italian incident of 1900 (p. 97), but because it contained toxin derived from the blood of a horse in the incubation period of tetanus.

In October 1901, twenty children became ill with tetanus and fourteen died after injection with diphtheria antiserum supplied by the Health Department of the city of St Louis. Eight of them were dead within 6 days. A special commission was appointed by Dr M. C. Starkloff, the health commissioner, consisting of Dr B. Meade Bolton, Director of the Marion-Sims-Beaumont Pathological Laboratory at St Louis, Dr E. C. Walden of the J. T. Milliken Company, and Dr Carl Fisch, a local pathologist. Their report was issued on the 23rd November 1901 (Bolton *et al.* 1901).

According to this report diphtheria antiserum was prepared by the city bacteriologist, Dr Amand Ravold. The horse in use at the time was one called Jim. It had been used for this purpose for nearly three years and had furnished thirty litres of antiserum. On 10 August 1901, it was injected with 800 ml of diphtheria toxin and on the 24th it was bled, ten litres being removed. On 22 September, it was again injected with diphtheria toxin, and on the 30th it was bled, eight litres being removed. On 2 October, it showed commencing signs of tetanus and was killed.

The city bacteriologist asserted that the serum from the bleeding of 30 September was poured away, but the commissioners reached other conclusions. Their observations showed that the serum responsible for the cases of tetanus in the injected children was bacteriologically sterile but contained tetanus toxin. Part of this serum was labelled 30 September, and part 24 August. There were two lots of serum labelled 24 August; one was toxic, the other was not. It seemed clear, therefore, that some of the serum from the bleeding of 30 September had been mixed with some of the serum of 24 August, or had been given this date on its label, and that both these lots of serum contained tetanus toxin. The horse must have had tetanus toxin in its blood two days before it showed symptoms of illness.

The commissioners pointed out that the serum of 30 September must have been issued before it could even have been tested for antitoxic potency against diphtheria. This conclusion was reinforced by their obtaining on 1 November some serum dated 23 October. Proper animal tests could not have been carried out in such a short time. Had diphtheria antitoxin potency tests been performed on the serum of 30 September, the guinea-pigs would have died of tetanus and the serum would not have been issued. These conclusions were accepted by the city coroner and his two deputies when they signed their verdict (Report 1901).

After this verdict another commission was set up composed of the mayor of St Louis, the health commissioner, the president of the City Council, two medical members of the Board of Health, a police commissioner and three lay members of the council. At their second meeting on 10 December the statement by Dr Ravold, the city bacteriologist, that the serum from the bleeding of 30 September had been discarded was contradicted by Martin Schmidt, the assistant city bacteriologist. According to Schmidt (1901) he had been directed on 3 October by Dr Ravold to prepare for distribution the serum withdrawn from the horse Jim on 30 September. He also asserted that the serum was distributed to physicians without being tested on guinea-pigs. That the conditions in the city laboratory were very irregular was further made clear by his statement that serum was kept unlabelled in the ice-box, and that the drawings of different dates were identified only in the mind of the unqualified janitor.

Two of the members of the first commission, Dr B. Meade Bolton and Dr Carl Fisch (1902), after their report had been published, carried out some experiments on horses to determine how long tetanus toxin is demonstrable in the blood before clinical signs of the disease appear in the animal. There is no need to describe these in detail. Suffice it to say that three horses were inoculated experimentally with tetanus spores and that a fourth horse, accidentally infected, was also studied. The results showed that tetanus toxin may make its appearance in the blood of a horse 3 to 4 days before symptoms of tetanus are evident. It increases in amount to reach its maximum 2 days before symptoms are evident, and then diminishes fairly rapidly, and sometimes even disappears, before death.

The horse providing the toxic diphtheria antiserum was bled 2 days before the onset of symptoms, at a time when the tetanus toxin content of the blood was probably at its height. The serum contained sufficient tetanus toxin to kill a guinea-pig in a dose of 0.1 ml. Taking the susceptibility of human beings to tetanus toxin as 0.85 that of a guinea-pig, Bolton and Fisch calculated that on a weight-for-weight basis the fatal dose for children would have been about 10 ml.

6

FAULTY PRODUCTION: USE OF WRONG CULTURE

The Lübeck disaster, 1930

The catastrophe that occurred at Lübeck in 1930 following the vaccination of newborn infants with BCG was of a different nature from any of the incidents so far reviewed. With very little doubt it was due to the admixture of a strain of virulent human tubercle bacilli with the vaccinal strain. It formed the object of an extensive investigation by some of Germany's foremost pathologists, and of a judicial trial by the Superior Court of Lübeck of those who were responsible for the preparation of the vaccine.

The official report of the commission specially appointed by the German government was not published till five years after the event (Report 1935). It was thorough, extensive, and occupied over 400 quarto pages of print. The pathological section alone, as distinct from the bacteriological, was the result of the work of two pathologists assisted in one way or another by 58 other medical men. In addition to the official report, numerous papers were published by other investigators, particularly in Germany and France; and the whole incident was closely followed by the medical press in different countries of the world. There is no need here to review the evidence in detail, but the history is briefly as follows.

Between 10 December 1929 and 30 April 1930, 251 of 412 infants born in the old Hanseatic town of Lübeck received three doses of BCG vaccine by the mouth during the first ten days of life. Of these 251, 72 died of tuberculosis, most of them in two to five months and all but one before the end of the first year. In addition, 135 suffered from clinical tuberculosis but eventually recovered; and 44 became tuberculin-positive but remained well. None of the 161 unvaccinated infants born at the time was affected in this way and none of these died of tuberculosis within the following three years.

Three of the 251 vaccinated children had been vaccinated between 9 December 1929 and 10 February 1930. The main series of vaccinations did not start till 24 February 1930. Two of the three children suffered from tuberculosis—thought to be congenital—and the third became tuberculin positive.

As might be expected after oral administration, the lesions were mainly in the alimentary tract, but in some infants the lungs were primarily infected. The reason for such an unusual manifestation was that at the time of administration of the vaccine the nose of refractory infants had been compressed by the nurse so as to make them swallow the fluid. As a result the vaccine was partly inhaled and gave rise to primary lesions in the lungs as well as in the alimentary tract. Many of these infants also suffered from a primary middle-ear complex. Nearly all the infants having a primary lung complex died.

Post-mortem examination showed the presence of primary lesions in the intestine of 71 out of the 72 fatal cases. The lower part of the small gut with its associated mesenteric lymph glands was chiefly affected. Diarrhoea was less prominent than anorexia and vomiting. Later, in the

more severe cases, the cervical glands reached the size of a hen's egg and caused interference with respiration and swallowing. There developed high intermittent fever, enlargement of the spleen, an extreme degree of anaemia, prolonged vomiting, profuse diarrhoea, and very severe meteorism caused by multiple strictures of the gut resulting from strangulation by adhesions or by pressure from swollen mesenteric lymph glands. Other symptoms seen in some cases were intestinal haemorrhage, peritonitis, or jaundice due to compression of the common bile duct. Palpable tumours were unusual. Tubercle bacilli were sometimes found in the faeces, but the evidence on their frequency is discrepant, some observers saying often, others seldom.

Thirty-five per cent of the patients suffered from a toxic tuberculous hepatitis, which went on in the survivors to cirrhosis. Calcification in the mesenteric glands was visible radiographically in 1½ to 3 years. In primary lung disease coughing appeared to be due mainly to compression of the bronchi by swollen mediastinal lymph nodes. In the few infants that survived this form of tuberculosis, calcification of the thoracic lymph nodes was visible in 1¾ to 2¼ years.

It is interesting to note that erythema nodosum was never observed and that lesions of the skin—tuberculides—and of the subcutaneous tissue—scrofulodermia—due to metastatic implantation of bacilli—were uncommon.

The tuberculin reaction became positive in 3 weeks to 3 months. The earliest positive reaction was noted in one infant on the 23rd day; then followed one on the 27th, two on the 28th, two on the 33rd, and one on the 34th day. At first, the reaction was to 0.1 ml of 1/100 Old Tuberculin, but by four to five months most infants reacted to a 1/100 000 dilution, and a few to 1/10000000. Lesions were also present in the large intestine in about two-thirds of the infants, but appeared to be secondary. The small gut was ulcerated, the number of ulcers ranging from one to seventy. The mesenteric lymph glands were enlarged and caseous; some showed early evidence of calcification. Other lymphatic glands in the abdomen, such as the aortic and pancreatic-duodenal, were also involved.

In 27 cases tuberculous lesions, many of them post-primary, were present in the stomach, and in 11 cases the stomach was ulcerated.

In 89 per cent of the cases coming to post-mortem the cervical glands were affected as the result of lesions in the lymphatic tissue of the tonsils or nasopharynx or in the middle ear.

A primary lung complex was found in 15 of the 72 infants that died of tuberculosis.

The 72 deaths from tuberculosis occurred between 44 and 498 days. Of these, 21 infants died of generalized tuberculosis in between six weeks and six months; 17 of tuberculous meningitis in between two and a half and ten months; 12 of intestinal obstruction caused by multiple adhesions in the gut; 8 of peritonitis; 4 of anaemia; 3 of secondary infection; and 6 from miscellaneous causes.

CLINICAL MANIFESTATIONS

Clinical illness, when it occurred, was almost invariably manifest in 4 to 8 weeks. The symptomatology of primary tuber culosis of the alimentary tract was very variable. In general, the infants failed to thrive in spite of breast-feeding. They suffered from mild febrile attacks, vesicular eruptions, and swelling of the cervical glands.

It was noted that groups of infants vaccinated with the same batch of BCG had similar clinical findings, but that there was great variation

between different groups. Judged by the degree of severity of the disease in the vaccinated infants, the vaccine seemed to be most virulent during the last week of February and the first four weeks of March. Then came ten days during which it was comparatively innocuous, followed by three days of renewed virulence; and finally a fortnight in which it showed a great decline in virulence. The retrospective bacteriological inquiry undertaken by Dr Ludwig Lange and others lent support to the general conclusion that the virulence of the vaccine varied according to the batch.

BACTERIOLOGICAL EXAMINATION OF CULTURES

Ludwig Lange and his colleague Hildegard Pescatore (1935) examined sixteen cultures from Deycke's laboratory at Lübeck. Eleven of them were cultures of the BCG strain. Two were strains of human type isolated from cases of tuberculosis and used for virulence tests in the laboratory. Three cultures, referred to as belonging to the Kiel strain, were virulent strains of the human type used for the preparation of 'Partigen' and came originally from the Robert Koch Institute at Berlin.

These strains were subjected to extensive animal tests. The results were not always easy to interpret, and are difficult to summarize in a short space. Broadly speaking, however, one of the BCG strains was found to be partly virulent for guinea-pigs, killing them in 2—5 months with fairly widespread lesions. The reactions, however, to this strain were irregular, suggesting that it contained a mixture of virulent and avirulent bacilli. The Kiel strains were distinguished by the production in two to four weeks of a characteristic greenish-yellow fluorescence in Sauton's medium. This property was not lost on passage through guinea-pigs. Examination of 30 other strains of human type failed to reveal any capable of giving a green growth in culture.

Remains of the vaccine were obtained From various quarters, but only three samples yielded growth of tubercle bacilli. One sample contained only avirulent BCG bacilli. Another sample contained avirulent BCG bacilli, but one or two of the guinea-pigs inoculated with it died of generalized tuberculosis caused by a bacillus of the bovine type; this was considered to be due to a spontaneous infection of the animals, though where the bovine strain came From is not explained. The third sample contained virulent human bacilli of the Kiel type.

From 28 dead children and From the cervical glands of one living child virulent bacilli having the characters of the Kiel strain were cultured. From two dead children and From the stomach washings of one live child avirulent strains were isolated, though in one of the strains virulent bacilli of the Kiel type were demonstrated in very small numbers.

Whether the virulent bacilli in the vaccine were due to contamination or were genuine bacilli of the BCG type that had become virulent by growth in the media used in the Lübeck laboratory presented a difficult problem For solution. The second alternative was rendered not improbable by the observations of Petroff and his colleagues in the United States (Petroff 1927, Petroff and Branch 1928, Petroff, Branch and Steenken 1927, Petroff and Steenken 1930), and of Watson (see Watson 1933) in Canada, both of whom had found BCG to be unstable and capable of regaining its virulence for animals. All attempts, however, on Lange's part to increase the virulence of the Lübeck BCG strain by cultivation on various media and by animal passage failed completely.

The fact that the virulent bacilli possessed the unusual property of greening when grown in Sauton's medium pointed strongly to the probability that the Kiel strain had been incorporated in greater or lesser

degree in some of the batches of the vaccine. That this was not unlikely was attested by the fact that the Kiel strain was kept in the same room as the BCG strains and even, at one time, in the same incubator.

The findings of Ludwig Lange were in general accord with those reached by independent investigators at the Robert Koch Institute in Berlin (B. Lange 1930a, *b)* and of Hahn (1932) at the Hygienic Institute of Berlin University. The strains isolated from the children conformed in their cultural properties—particularly their production of greening in Sauton's medium—in their chemical structure—lipid content—and in their behaviour in animals with the Kiel strain of virulent human-type bacilli.

THE TRIAL

It was inevitable that proceedings would be taken against those who were held responsible for the catastrophe. In this the public prosecutor was supported by all the parents of the children who had suffered from vaccination. The trial opened on 12 October 1931 before the Superior Court at Lübeck and lasted till 6 February 1932. Over seventy sittings were held, and at one time the Court adjourned to the laboratory where the vaccine was made.

The first three months were occupied mainly in the hearing of witnesses. Medical experts were given free rein to express their views, and the court at one time resembled a medical forum. As already indicated, the real question at issue was (a) whether the strain of BCG received by Deycke from Calmette in Paris was virulent at the time of its arrival or had become spontaneously virulent since; or (b) whether the vaccine had become contaminated with a virulent strain in the laboratory. Hans Much of Hamburg and Uhlenhuth the veterinarian from Freiburg, without committing themselves completely, both gave evidence in favour of the former alternative: Bruno Lange of the Robert Koch Institute in Berlin, Ludwig Lange of the Imperial Health Office, Wilhelm Kolle of the State Institute For Experimental Therapy in Frankfurt-am-Main, and Martin Hahn of the Hygienic Institute of Berlin University, among others, discountenanced this explanation and insisted that a virulent strain of tubercle bacillus had gained access to the vaccine. The bacteriological evidence was undoubtedly conflicting, and even the carefully conducted virulence tests reported by Bruno Lange and Ludwig Lange had given partly equivocal results.

Three medical men were on trial—Dr Georg Deycke, medical superintendent of the Municipal General Hospital; Dr Ernst Alstaedt, an old pupil of Deycke's, who was medical director of the Lübeck Health Office; and Dr Max Klotz, chief physician to the Children's Hospital. In addition Fräulein Anna Schütze, a laboratory attendant without medical qualifications, was placed in the dock.

It was alleged that Dr Deycke, who was 66 years old, and an experienced bacteriologist and tuberculosis expert, had been negligent in the preparation of the vaccine. He had entrusted it to the unqualified laboratory attendant; he himself seldom visited the laboratory. Though the Imperial Health Office at Berlin had been informed that the strain of BCG had been tested for virulence, it transpired that neither the strain nor the vaccine prepared from it had ever been injected into guinea-pigs. The vaccine, which might quite easily have been obtained from the Pasteur Institute in Paris, had been prepared in odd batches by Fräulein Schütze, working in the evening after her routine duties were over. No special laboratory had been set aside for it. The work was carried out in the entirely unsatisfactory environment of an ordinary hospital laboratory.

Incubators were not locked; virulent and avirulent strains of tubercle bacilli were kept in the same room and sometimes in the same incubator; culture tubes were identified by sticky paper labels which occasionally fell off and had to be replaced; the BCG strain was grown on a solid egg medium, with or without added haematin, instead of in the fluid Sauton medium recommended by Calmette; the records were unsatisfactory; and no steps were taken to check the harmlessness of the final product. Moreover, as soon as Professor Deycke realized that something had gone wrong, he destroyed the cultures and the vaccine in his laboratory.

Incidentally, for the sake of clarity, it should be explained that, though this destruction hampered the investigation, it was not complete; some living cultures were later discovered in the laboratory which were examined by Bruno Lange and Ludwig Lange. In addition, of course, numerous cultures became available from the fatal cases, and a few from tuberculous infants that were still alive.

Dr Alstaedt was accused of negligence in acting against the advice given in January 1927 by the Imperial Health Office, namely to postpone vaccination with BCG till further information was available about its harmlessness and its protective power; in failing to inform the Imperial Health Office that he intended to introduce BCG vaccination at Lübeck; and in not stopping the distribution of vaccine as soon as it became evident that its administration was harmful.

Dr Klotz was accused of negligence in not keeping the vaccinated infants under surveillance.

At one time the court was told that a similar catastrophe had occurred at Pernik in Bulgaria where 75 out of 280 children had died after vaccination and 111 had become seriously ill. No official confirmation of this statement of Deycke's was forthcoming.

The long-drawn-out spectacle of the trial resembled an ancient Greek tragedy, played between the doctors and the fates, pursuing its way relentlessly to its climax of horror and death, and watched by a crowd of parents who served as the chorus, uttering their dismay whenever the emotional atmosphere became too tense.

Professor Deycke and Dr Alstaedt were both found guilty of manslaughter by negligence in 68 cases and of injury by negligence in 131 cases. Sentence of 1 year and 10 months imprisonment was passed on Professor Deycke and of 15 months on Dr Alstaedt. Dr Klotz and Fräulein Schütze were acquitted, the charges against them not being proved sufficiently (see Kolle 1932).

Thus ended one of the worst disasters in the history of preventive inoculation. Besides the opportunity it afforded of studying the development and progress of tuberculosis in infants experimentally infected by the mouth at a known time with virulent tubercle bacilli of human type, the episode revealed the importance of keeping any partly or completely avirulent strain of microbial nature intended for vaccination entirely separate from more virulent strains, and had the effect of tightening up precautions taken by manufacturing laboratories engaged in the preparation of live vaccines. This was all to the good, but it was a heavy price to pay for the taking of what should have been self-evident precautions. Dr Deycke realized this and in a moving speech at the last session of the court asked that, if the court decided that punishment was deserved, it should fall on him alone and that the others should be held free of blame.

It is hardly necessary to point out that, had it not been for the characteristic greening property of the Kiel strain, the source of

contamination of the vaccine would have remained obscure; and the possibility that variant bacilli in the BCG strain had become virulent would have been more difficult to refute.

Experience during the 35 years that have elapsed since the Lübeck catastrophe has not modified the conclusions reached in the official report. Several million infants have now been vaccinated with BCG and, apart from a few exceptional cases (see p. 242), have suffered no serious permanent injury. The general verdict of bacteriologists at the present day is that, though different strains of BCG held by laboratories in different parts of the world vary somewhat in their degree of attenuation, none of them is capable, except quite rarely, of setting up progressive tuberculosis when injected into human beings. For all practical purposes BCG vaccine can be regarded as safe, provided that it is used with caution in infants and is not administered to tuberculin-positive subjects.

7

FAULTY PRODUCTION: BACTERIAL CONTAMINATION OF VACCINE OR ANTISERUM

IN DEALING with accidents that have followed the use of vaccines or antisera contaminated with various micro-organisms it is sometimes difficult to distinguish between contamination occurring at the time of production and contamination resulting from imperfect technique used by the operator in giving the injection. I have decided, rather arbitrarily perhaps, to include in the former group those accidents in which, though contamination may have been introduced by the operator, no ill effect would probably have resulted had not the vaccine been defective in its failure to contain an antiseptic. Among the bacteria that have caused most trouble are the staphylococci, and I shall therefore begin my account with them.

STAPHYLOGOGCAL CONTAMINATION

Typhoid vaccine: Columbia, S. Carolina, 1916

In this incident a number of persons injected with a particular batch of typhoid vaccine suffered from unusually severe reactions caused by contamination of the vaccine with *Staphylococcus aureus.* Four of the cases, all in children under five years of age, proved fatal, and many of the others suffered from local abscess formation.

The anti-typhoid vaccine, lot 67, had been prepared in the laboratory of the State Board of Health, found to be sterile, and kept in bulk in the refrigerator. Before use it was filled by hand into vials fitted with rubber stoppers. Since only part of lot 67 proved toxic, it is presumed that contamination of some vials took place during the filling process. After distribution, it was kept by practitioners at room temperature, which was high at the time, thus allowing any contaminating organisms ample opportunity for multiplication.

Though contamination probably occurred during filling, it should be mentioned that in order to take up vaccine into the syringe at the time of injection the practitioner had to remove the rubber cork from the vial. This was replaced if sufficient vaccine was left in the bottle for use on another day, thus adding to the chances of contamination and bacterial growth.

The vaccine was used for injecting both children and adults. From the returns of practitioners after the deaths had occurred, the following figures were compiled.

Number of persons injected	322
Number under 5 years of age	37
No reaction	10
Usual reaction	244
Severe reaction	68
Local abscesses	26
Deaths	4

It will be seen that rather less than a third of those injected reacted abnormally.

The history of the four children that died may be briefly given.

Case No. 1. Aged 2½ years. Injected with 2 minims (0.12 ml) at 11 a.m. Child became febrile about 11 p.m., and at 6 the following morning it began to suffer from nausea, vomiting, cyanosis and intestinal paresis. It gradually grew worse. Coma and convulsions supervened, and death occurred 31 hours after injection.

Case No. 2. Age 4½ years. Injected with 3 minims (0.18 ml) at 11 a.m. At 6 p.m. it began to suffer from nausea, vomiting and cyanosis. Became comatose at 4 the next morning. Convulsions and intestinal paresis supervened and the cyanosis grew worse. Death occurred 19 hours after injection.

Case No. 3. Age 9 months. Injected with 10 minims (0.6 ml) at 4 p.m. When seen the next morning it was cyanosed. Gradually grew worse and died 23 hours after injection.

Case No. 4. Age 4½ years. Injected with 3-4 minims (0.18-0.24 ml). Awoke nauseated at 1 the next morning. Had a temperature of 104°F, vomiting and diarrhoea. Improved temporarily, then relapsed. Diarrhoea returned. Became cyanotic about 2 p.m. and later unconscious. Pulse 160. Had convulsions at 4.30 p.m. and died at 5 p.m.—presumably 18-24 hours after injection.

No post-mortem examinations were made.

The parents of these children were injected with the same lot of vaccine at the same time by the same practitioner, but suffered from only moderate reactions. In the absence of information on the size of dose given to the parents and the children, it is impossible to say what the susceptibility on a weight-for-weight basis of children and adults is to staphylococcal toxin; but it is clear that children are in greater danger of experiencing a severe reaction after receiving a given amount of toxin than are older persons.

Two children injected at the same time as case 3 had a severe reaction with high temperature, swelling of the extremities and mucous membranes, a dark red rash and convulsions.

Two children under five and three over five years of age, together with several adults, were injected with the same lot of vaccine by the practitioner in charge of case 4. None of them experienced a severe reaction. This suggests that a different vial of vaccine was used than that for case 4.

When the trouble was reported practically the whole of this lot of vaccine was exhausted but unused portions were obtained from the practitioners in charge of cases 1 and 2. Aerobic and anaerobic cultures yielded *Staph. aureus.* So also did an unused vial of 5 ml of vaccine.

The onset of illness, the symptoms, and the time to death in the four fatal cases were very similar to those in the children that died in the Bundaberg incident of 1928 (see p. 78) when a diphtheria toxin-antitoxin mixture contaminated with *Staph. aureus* was used for injection.

No official publication appears to have been issued on the Columbia incident.

Diphtheria TAM: Bundaberg, Queensland, 1928

This disaster, in which 12 out of 21 children died after injection with diphtheria toxin-antitoxin mixture, was studied by a Royal Commission,

set up with commendable promptitude four days later, and received a more thorough investigation than any similar incident before or since with the single exception of the Lübeck disaster. The report (1928*a*) of the Royal Commission was published within five months and was widely commented on in British and foreign journals (Annotations 1928). Numerous experiments were carried out in the laboratory to exclude various possibilities, other than the obvious one of staphylococcal contamination of the TA mixture, such as metallic poisoning, food poisoning, tetanus, dissociation of the toxin-antitoxin components, and infection with other organisms, which do not warrant a detailed description here. It will be sufficient to give the main facts, the conclusions drawn from them, and the recommendations made by the Commissioners—Dr C. H. Kellaway, Director of the Walter and Eliza Hall Institute of Research, Melbourne, Professor P. MacCallum, Head of the Department of Pathology of the University of Melbourne, and Dr A. H. Tebbutt, Pathologist of the Royal Prince Alfred Hospital, Sydney.

DESCRIPTION OF THE INCIDENT

In January 1928, in the early stages of an immunization campaign against diphtheria, Dr Ewing George Thomson, Medical Officer of Health of Bundaberg, began the injection of children with toxin-antitoxin mixture. The material was taken from an indiarubber-capped bottle containing 10 ml of TAM prepared on 5 September 1927 by the Commonwealth Serum Laboratories, Melbourne. It belonged to batch 86 and contained no antiseptic. The bottle used by Dr Thomson was sent off to him from Medical and Surgical Requisites Ltd, Brisbane, on 6 January 1928, and was stored in an instrument cupboard in his surgery. There was no marking on the bottle or any accompanying notice to draw attention to the absence of a preservative agent.

On the 17th, 20th, 21st and 24th January, Dr Thomson injected subcutaneously a total of 24 children without ill effect. On the 27th a further 21 children were injected between 4 and 5 p.m.—thirteen for the first time with a dose of 2 minims and eight for the second time with a dose of 4 minims. Of these children, whose ages ranged from 11 to 9½ years, eighteen became ill during the same night or early the next morning. Eleven died on the 28th and one on the 29th, all within 15-25 hours of the injection. Of the eight children receiving the larger dose, six died, and two recovered after a severe illness. The morbidity and case fatality rates in this group were both higher than in the group of thirteen children injected for the first time, with the smaller dose, of whom six died and four recovered after a more or less severe illness. In all the children that survived, including the three in the second group that were not ill, abscess formation occurred at the site of the injection.

Symptomatology

The onset of symptoms was between 9.15 p.m. on 27 January and 1 a.m. on the 28th, i.e. 5-8 hours after the injection. The first symptom was vomiting followed by diarrhoea with the evacuation of several loose foul-smelling stools. Both these symptoms ceased early, but in many cases vomiting recurred before death, probably as a result of bulbar toxaemia. Pallor, collapse, and unconsciousness were prominent features. Both the pulse and the respiration rate were extremely rapid and out of proportion to the temperature. Retention of urine was common, but passed off rapidly in those that recovered. The general picture was one of profound

circulatory collapse associated in the terminal stages with deep blotchy cyanosis and convulsions. A rash on the body was observed in two of the cases. There was no evidence of oculo-motor or other paralyses or of meningitis. The local abscesses that formed in the survivors contained staphylococci.

Post-mortem findings

Nine autopsies were performed but the examinations were not very thorough or the findings very revealing. There were no gross macroscopic lesions. There was said to be congestion of the spleen, the meninges and the surface of the brain. Histologically, there was general swelling and hyperplasia of the lymphoid tissue, with proliferation, desquamation and phagocytic activity affecting the endothelial cells in the lymph node sinuses, and degeneration of the lymphocytes and endothelial cells in the malpighian corpuscles of the spleen. The adrenals appeared normal. Cocci were visible in most organs, but their distribution among the tissues could not be satisfactorily determined.

Examination of the bottle of toxin-antitoxin mixture

There was abundant evidence that the batch of TA mixture to which the bottle used by Dr Thomson belonged had been prepared satisfactorily, was non-toxic, and was free from bacterial contamination when it was distributed. Moreover the fact that the same bottle was used uneventfully by Dr Thomson for injection on the 17th, 20th, 21st and 24th January indicated that something had happened to it between the 24th and the 2 7th. Dr Thomson himself said that the fluid contained in it was clear on the 27th but was cloudy on the morning of the 28th. Cultivation revealed the presence of *Staphylococcus aureus,* giving haemolysis on a blood-agar plate, and identical so far as could be judged by cultural, serological, and bacteriophage tests with the staphylococci isolated from the abscesses of the surviving children. Both strains were of low pathogenicity to guinea-pigs, mice and monkeys, but were sometimes fatal in 12-24 hours to rabbits injected intravenously. When grown in a toxin-antitoxin mixture similar to that of batch 86 and injected in small doses intravenously into rabbits, the organism caused death with convulsions in as short a time as 11 hours. A filtrate of a blood broth culture diluted 1/500 to 1/2000 gave rise to a skin reaction in susceptible children.

The temperature at which the bottle was stored in Dr Thomson's surgery was between 70^0 and 8o°F. In all probability the contents were contaminated during use on the 24th. That organisms may have gained access to the interior through the hole made by the needle puncture in the rubber cap was shown by the demonstration, in the contents of the bottle, of traces of iodine which had been used for sterilizing the surface of the cap. Where the organisms came from is debatable. The syringe and needle had been 'sterilized' in methylated spirit, from which they were transferred to sterile water and assembled by Dr Thomson's hands without the use of forceps. The organisms may therefore have been derived from an imperfectly sterilized syringe or from Dr Thomson's fingers. Alternatively they may have been introduced with the air injected into the bottle by the syringe before withdrawal of the contents. Experiments showed that with a rigid technique air could be introduced in this way without contamination, provided the air of the room was still; but that, if the air was disturbed by a fan, contamination became almost inevitable. In whichever way the

contamination had occurred, there seems no doubt that by the 27th the staphylococci had multiplied sufficiently to render the fluid toxic.

Dr Burnet, who carried out experiments on the growth of staphylococci in TA mixture, concluded that at the time of injection there must have been a concentration of from 1 million to 40 million staphylococci per ml. Children, therefore, who were injected with 2 minims (0.12 ml) must have received somewhere between 130 000 and 5 million organisms. These estimates are both extremely conservative, and the numbers may well have been much higher.

Explanation of the symptoms

The Royal Commission spent a great deal of time and thought in an attempt to understand the pathogenesis of the illness. They were satisfied that death had occurred from toxaemia, but they were at a loss to explain the extremely rapid evolution of the disease. In the numerous instances in which staphylococci had been experimentally injected under the skin in man, little more than localized abscesses had resulted. Why was it that in this instance symptoms of general illness were noticeable within a few hours and that all the deaths occurred within 25 hours? A few cases are quoted of acute staphylococcal osteomyelitis or other disease originating in trauma that proved fatal in 24 to 48 hours, but these are regarded as exceptional.

The Commission made a rather surprising statement: 'It is inconceivable that sufficient staphylococcal toxin could be produced *in vitro* in the toxin-antitoxin mixture to account for the symptoms. Massive production of toxic substances *in vivo* must have taken place in the fatal cases if staphylococci were the responsible agents.' This reasoning is a little difficult to follow. If the mixture, which contained nutrient broth and was free from antiseptic, was contaminated on the 24th and kept for 3 days at a temperature of 70-80 °F, quite a large amount of toxin may have been formed. We know that under such conditions an enterotoxin-forming strain of staphylococcus can produce a toxin of sufficient potency, when ingested, to cause an illness very similar to that experienced by the Bundaberg children, namely severe vomiting, and often diarrhoea, coming on within 2-6 hours, followed by profound circulatory collapse and coma. It is true that death seldom occurs in these cases of acute staphylococcal food poisoning, possibly because much of the toxin ingested is removed by vomiting and diarrhoea from the intestinal tract before massive absorption into the tissues has had time to take place; but if toxin by the mouth can produce such an illness verging on the fatal, it requires no great stretch of the imagination to picture what might happen if a powerful staphylococcal toxin was injected into the tissues. This does not mean to say, of course, that the staphylococci did not multiply in the body after injection. They may well have done so and produced considerably more toxin, thus contributing to the fatal outcome. The fact, however, that symptoms of general illness were evident in some children 5 hours after injection points to the presence of preformed toxin in the TA mixture.

The Commissioners realized that the circumstances were exceptional; that the subcutaneous injection of large numbers of living staphylococci had probably never been made before; and that they had no experience to guide them on what the result would be. They were not, of course, as familiar as we are now with the pathogenicity of the staphylococcus. They were conducting their investigation at a time when this organism was regarded more as a nuisance than as a serious enemy of man. They had not

seen acute staphylococcal food poisoning or the rapidly fatal cases of staphylococcal pneumonia which characterized the influenza epidemic of 1957. Their hesitation, therefore, in concluding that the illness was entirely of staphylococcal origin is fully understandable, and they certainly did right in excluding every other possible agent. The final sentence in the summary of their findings reads as follows:

The consideration of all the available evidence concerning the deaths at Bundaberg points to the injection of living staphylococci as the cause of the fatalities.

No mention is made of preformed toxin in the TA mixture, nor is any attempt made to explain why, in the absence of preformed toxin, symptoms could have come on so rapidly. Experience shows that patients infected with staphylococci in the operating theatre exhibit, as a rule, no signs of general illness—if indeed anything more than a local abscess develops—for a day or two at least; and even if it is assumed, as is improbable, that the number of organisms introduced into the wound is as great as that injected into the Bundaberg children, it is very unlikely that they would become ill within 5 hours of leaving the theatre. It would probably be better to amend the Commissioners' findings to a statement such as:

The consideration of all the available evidence concerning the deaths at Bundaberg points to the injection of a toxin-antitoxin mixture in which staphylococci had been growing for some days and produced a powerful toxin. This toxin, probably combined with the production of further toxin in the body, was responsible for the severity of the disease and the rapidly fatal issue.

Recommendations

Among the recommendations in the report of the Royal Commission is the very important one that biological products in which the growth of pathogenic organisms is possible should not be issued in rubber-capped containers for repeated use unless there is present in the material a sufficient concentration of antiseptic to inhibit bacterial growth. Biological products not containing antiseptic should bear a conspicuous printed notice, both on the container and on the package, to the effect that no antiseptic is present; they should be used immediately on opening and any remaining product should be discarded.

Before the accident occurred the Commonwealth Serum Laboratories at Melbourne realized the danger of what they had done in omitting antiseptic from their preparation of toxin-antitoxin mixture and sent a telegram to the Commonwealth Health Authority at Brisbane requesting that each doctor to whom the prophylactic had been supplied should be notified that it contained no antiseptic and that a bottle once opened should therefore not be reused later. In Brisbane, instead of wiring or telephoning each doctor concerned immediately, the Health Authority prepared a printed slip conveying the necessary warning, and gave instructions that a copy of the slip was to be enclosed with the usual monthly account which would be sent to anyone who had obtained one of the bottles containing the prophylactic agent. In most instances, including that of Dr Thomson, this warning did not arrive till after the agent had been used and reused.

It is not surprising, therefore, that when the Commissioners examined 31 bottles of batch 86 which had been used by practitioners for injection they found that nine of them—about 30 per cent—contained living bacteria. This shows how easy it is for rubber-capped containers to become contaminated, either through puncture holes in the rubber cap or by air introduced into the syringe.

Staphylococcal sepsis after use of smallpox vaccine at Malmö, 1932

Infection with alastrim was introduced into Sweden by a stonemason who returned from Soviet Russia to Malmö on 4 December 1931. Only one secondary case occurred, but after the appearance of eight tertiary cases at the end of January 1932 mass vaccination was decided on. The population of Malmö was 130 000. Of this total, 116 000 were deemed to be at risk and were offered vaccination; 97 per cent, i.e. about 112 000, accepted (Höjer 1932).

Shortly after vaccination had begun, complaints were received of severe local reactions accompanied by regional adenitis and often fever. Instead of the normal vaccinal reaction beginning to subside after the 10th day with a scab forming about the 14th day and becoming detached during the 4th week, constitutional symptoms appeared, the crusts became hard, black, and adherent, and the lymphatic vessels were inflamed. The lesions were up to 4 cm in diameter, penetrated into the underlying flesh—often to the muscle layer—and when the crusts ultimately separated they left beneath them a quantity of pus contained in deep granulating cavities that filled up very slowly. Healing was not complete for 2-5 months after vaccination.

Though urged to do so, the local authority failed to institute any inquiry into the number of persons affected, so that it is impossible to tell the real extent of the damage. Magnusson (1932) estimates the attack rate at about 10 per cent, making a total of over 10 000 persons; but Kling (1933), who was responsible for making the vaccine, discredits this and points out that at the public hospital in Malmö only 70 cases of post-vaccinal necrosis were treated. According to Forssman (1932*b*), however, several hundred patients were treated at the City Health Centre itself, in addition to those under the care of their own general practitioner. It seems clear that a large number—probably some hundreds and possibly thousands—of persons were seriously affected, that adults suffered more than children, and that old persons suffered most of all.

The vaccine used had been prepared at the State Bacteriological Institute from young heifers. The pulp had been suspended in pure glycerol in the ratio of 1:3, kept for 3-4 weeks at a temperature of 6-8°C, and thereafter at -5°C. The batches issued at the time were 8-20 months old. Magnusson (1932), who examined several batches, found *Staphylococcus aureus* in numbers up to 67 000 per ml. In contrast, 21 vaccine lymphs from Denmark, Norway, England, Austria, Germany and Italy were free from this organism except for one batch from which a few colonies only were obtained.

Forssman (1932*b*), who examined four batches of vaccine, found *Staph. aureus* in numbers ranging from about 5000-10 000 per ml; in three of the batches this organism was present in pure culture. It was coagulase positive, and it produced typical renal lesions in rabbits injected intravenously with 0.2 ml of a broth culture.

A study of the organisms isolated from both the Swedish vaccine and the arms of patients showed that most of them were coagulase positive and were capable of giving rise to suppuration and severe necrosis when injected intracutaneously into horses, cattle, rabbits and dogs.

Davide (1933), who was Kling's assistant, contended that the staphylococci isolated from the vaccine were in no way different from the ordinary micrococci found in vaccine lymph. In support of this he relied partly on the fact that when injected intravenously into rabbits in a dose of 2 ml the various organisms behaved alike in killing the same proportion of animals; and partly on the finding that the staphylococci, when mixed with vaccine lymph and rubbed into the shaven skin of the rabbit, did not give rise to infection, either local or general. Magnusson (1933) agreed with this second observation, and insisted that in animals staphylococci must be injected intracutaneously if they were to cause suppuration. He criticized Davide's intravenous test of pathogenicity on the ground that 2 ml is such a massive dose that any coccus, pathogenic for man or not, might well prove fatal to a rabbit.

In the discussion of these findings there is no question that Forssman (1932*a*) was justified in expressing his horror at the distribution of vaccine lymph containing such large numbers of potentially pathogenic organisms. Vaccine lymph from other countries was found by Magnusson to be practically sterile; yet that issued by the State Bacteriological Institute at Stockholm had a colony count as high as 67 000 per ml. Indeed Davide (1933) admitted that vaccine had at times been sent out by the Institute containing more than 5 million bacteria per ml, though what proportion of these were staphylococci was not stated.

CONTRAST BETWEEN THE INCIDENTS AT MALMÖ AND AT BUNDABERG

It is worth while for a moment contrasting the Malmö incident with that at Bundaberg in 1928. In both incidents *Staphylococcus aureus* was concerned. At Bundaberg a diphtheria toxin-antitoxin mixture was used in which the organisms had been multiplying and produced a powerful haemolytic toxin; the material was injected into the tissues and caused the death of 12 out of 21 children. At Malmö no multiplication had occurred in the vaccine, so that no preformed toxin was present; moreover, the vaccine was inoculated on to the scarified skin, not injected subcutaneously. The result was that there were no deaths from septicaemia or toxaemia; but, with the exception of hepatitis after yellow fever vaccine in 1942 (see p. 117), the toll of persons affected, partly or wholly incapacitated as they were for 2-3 months by severe necrotizing local lesions, far exceeded that noted in any other single vaccinal catastrophe of whatever type.

It is also interesting to note that most of the victims at Malmö were adults. Attention has already been drawn, in discussing the Columbia incident of 1916 (see p. 77), to the apparently greater sensitivity of children than of older persons to the injection of staphylococcal toxin. Experience, both at Columbia and at Bundaberg (see p. 83), showed that staphylococcal toxin can often be lethal to children. Yet towards staphylococcal infection, at any rate on the surface of the skin, children seem to be less susceptible than adults. Why this should be so, it is difficult to say. It may be that adults are more exposed to trauma than infants and very young children, and that they tend to suffer from a more severe reaction, both local and constitutional (Waddington *et al.,* 1964); or the reaction may be partly allergic, corresponding to the Arthus (1903)

phenomenon observed in rabbits that have become sensitized to staphylococci.

Observations similar to those made at Malmö on the greater susceptibility of adults to staphylococcal infection were repeated by Waddington and his colleagues (1964) during the South Wales outbreak of smallpox in 1962. About 900 000 persons were inoculated with vaccine lymph and 48 cases of severe local necrosis and ulceration were registered. Of these, no fewer than 45 were in adults. The description of the lesions closely resembles that of the cases at Malmö.

In conclusion, it must be assumed that in cases such as these the vaccinial lesion is infected with staphylococci, which gain access to it either in the vaccine lymph itself, as at Malmö, or through contamination from one source or another at the time of vaccination, or subsequently through trauma, contaminated dressings or other means.

Contamination of tuberculin with staphylococci

A fatal case of staphylococcal infection occurred in an infant injected intradermally with tuberculin (Olin and Lithander 1948). Four hours after injection the infant suffered from high fever, vomiting and diarrhoea; later spells of unconsciousness supervened, followed by circulatory failure and death in 17 hours. At post-mortem *Staph. aureus* was isolated from the local lesion and from an inflamed axillary gland. Of the ten other children who were injected with the same preparation many had similar symptoms but recovered. The tuberculin solution had been prepared at the hospital without the addition of any antiseptic and had stood for several hours daily in the outpatients' department. The strain of staphylococcus isolated killed a rabbit injected intravenously in a dose of 0.1 ml/kilog.

Contamination of convalescent measles serum with staphylococci

Olin and Lithander (1948) describe an incident in which three children injected intramuscularly at the same time with convalescent measles serum prepared at a hospital laboratory became ill within 6 to 8 hours. They suffered from high fever, vomiting and diarrhoea, followed by somnolence, agitation and cyanosis. Two of them died 14 and 18 hours after the injection. Post-mortem examination showed the presence of fatty degeneration of the liver and cloudy swelling of the renal convoluted tubules. From the empty bottle of serum a strain *of Staph. aureus* was isolated that formed abundant haemolytic toxin proving fatal to a rabbit inoculated intravenously in a dose of 0.5 ml/kilog. Presumably the serum had become contaminated from one of the workers in the laboratory in which the serum was prepared.

Renkonen (1948) in Finland described a similar incident in which three children were injected by a general practitioner with convalescent measles plasma from a bottle that had been used uneventfully 3 weeks before. The plasma contained no antiseptic. All three children rapidly became toxaemic and two of them died. *Staph. aureus* was isolated from the bottle.

CONTAMINATION WITH TETANUS BACILLI

Plague vaccine: The Mulkowal incident, 1902

In this incident, which occurred in India in October 1902, nineteen persons injected with plague vaccine contracted tetanus 5-6 days later and all died within 7-10 days of their injection. A special Commission, called the Punjab Plague Inoculation Commission, was set up by the Indian

Government to investigate the cause of the catastrophe. It consisted of the Honourable Sir Lawrence Jenkins, K.C.I.E., Chief Justice of the High Court of Judicature, Bombay; Lieut-Col. G. Bomford, C.I.E., M.D., I.M.S., Principal of the Medical College, Calcutta; and Major David Semple, M.D., R.A.M.C., Director of the Pasteur Institute, Kasauli. A confidential report was made to the Indian Government on 7 February 1903, but in the light of further evidence provided by Major Semple and Mr Haffkine, it was amended and resubmitted on 16 April 1903. It was never published, but is included in vol. 34 of the series of Revenue (Sanitary) Letters from India, at present kept in the library of the India Office, London. It forms the main substance of the following account.

In 1902 plague was very prevalent in the Punjab and a vaccination campaign was organized against it. A total of 505 849 persons were vaccinated. It was attended by a series of accidents, the first of which included abscesses and four deaths from undetermined causes and one death from tetanus—all apparently attributable to faulty technique in injection. Most serious, however, was the incident at Mulkowal. In this village 107 persons were injected with plague vaccine on 30 October. Of these, the first nineteen were affected with tetanus, which developed on the 4th and 5th November. The other 88 persons were unaffected. The first nineteen persons had all received vaccine from a single bottle marked 53N. The remainder were injected with vaccine from other bottles. Since it appeared that the same syringe had been used for injecting all 107 persons, with simple washing out in carbolic lotion in between the bottles, it was generally agreed that the vaccine in bottle 53N alone was contaminated with tetanus organisms.

Preparation of the vaccine

The vaccine had been prepared some weeks beforehand by Mr W. M. Haffkine at the Plague Research Laboratories, Parel, Bombay. Previously a broth vaccine had been made, but owing **to** the pressing demand for vaccine a water-agar preparation was substituted because it was quicker and easier to make. In the manufacture of this preparation the growth of plague bacilli on agar was washed off with saline water and the suspension decanted by means of a siphon into small bottles. The vaccine was heated to 65 °– 70 °C (for a time not stated) and then cooled by plunging the bottles into cold water, the corks being held in place by a special metal fitting. No antiseptic was added, and the bottles into which the vaccine was distributed were sent out after a small number had been sampled aerobically for sterility.

During the course of the Commission's inquiry this process was criticized by a number of bacteriologists who were working in India at the time, such as Captain W. G. Liston, Captain E. S. W. Greig, Dr M. Gibson, Dr N.F. Surveyor and Dr J. S. C. Elkington. In the first place the process of decanting was carried out by inexperienced lay assistants under conditions that invited contamination of the suspension. Secondly, it was held that, during the cooling process, some of the corks might easily become loosened and admit non-sterile water to the interior of the bottles. Thirdly, the removal of the metal fitting, at the time of injection, likewise often led to loosening of the corks with the consequent possibility of contamination from the fingers of the inexperienced lay assistants who performed the operation or from other sources. And fourthly, the absence of an antiseptic would allow any organisms, such as spore-bearing organisms, that had not been destroyed by the heating process, to multiply

at the atmospheric temperature at which the finished vaccine was held. The importance of this last point was strongly emphasized by Dr Elkington, who found that the number of contaminated bottles increased rapidly towards the end of October. In one consignment no less than 70 per cent had to be rejected for this cause.

In his defence Mr Haffkine, and the superintendent of the Plague Research Laboratory at Parel, Major M. B. Bannermann, I.M.S., admitted that the staff were largely untrained and that a certain amount of contamination of the vaccine was inevitable. Haffkine justified his omission of an antiseptic from the vaccine on the ground that (a) its addition would have necessitated an extra operation with consequent risk of contamination, (b) 0.5 per cent carbolic lotion would not have destroyed spore-bearing organisms in the vaccine, (c) it was by no means universal practice to carbolize biological preparations; for example, Professor Calmette in France did not carbolize his antivenene, nor did Professor Terni at Messina carbolize the anti-plague serum that he supplied to the Government of India; and (d) apart from Mulkowal, at least 100 000 injections with the new water-agar vaccine were made in the Punjab and 20 000 elsewhere in India without ill effect though a large number of the bottles were not sterile.

The injections

The injections at Mulkowal were carried out by Dr A. M. Elliot assisted by a compounder, Narindar Singh. Dr Elliot's account is not very easy to follow, but it seems clear that he relied on carbolic lotion (strength not stated but probably 5 per cent) for disinfecting his syringe and one minute's exposure in hot oil for his needles. The same syringe and possibly the same needle were apparently used for all 107 persons, the syringe being washed out with carbolic lotion in between each bottle. With each syringeful about 12 persons were injected, and two syringefuls were contained in one bottle. This suggests that the dose of vaccine for each person was about 1.5 ml, that the syringe held 20 ml, and that each bottle of vaccine contained about 40 ml. Whether three or four bottles were used is a little doubtful, but the point is of no great importance since only those injected from the first bottle, 53N, contracted tetanus. The compounder, in his evidence, said that the first bottle had a tightly fitting cork and that, in trying to remove it, the forceps he was using fell to the ground. He picked them up, 'swished' them in the lotion and then pulled the cork out with them. As the injections were carried out in the open air, the forceps must have been contaminated with soil dust. An important observation made by Dr Elliot was that, after the bottle had been opened, he smelt the contents but perceived nothing abnormal.

Bacteriological examinations

Subsequent examination of the bottle, 53N, at Kasauli revealed the presence of tetanus bacilli in the 0.5 ml residue. This finding was regarded by the Commission as indicating that tetanus bacilli must have been present in the bottle before it was opened at Mulkowal, since no multiplication of anaerobic organisms introduced at the time of opening could have occurred under the aerobic conditions existing in a practically empty bottle. This conclusion was questioned by Dr Charles Martin of the Lister Institute on the ground that, if ordinary saprophytic organisms had been present too, they might have rendered the conditions sufficiently anaerobic to enable tetanus bacilli to grow. Martin, however, refers to a

residue of 5 ml in the vaccine bottle, whereas in the Commission's report the more likely figure of 0.5 ml is mentioned. It is doubtful whether Martin would have contested the Commission's conclusion had he realized that the residue was only 0.5 ml—a quantity that would form but a thin layer at the bottom of the bottle in which anaerobic conditions would be very difficult to establish.

After carefully considering all the evidence, including the results of various experiments that were carried out for them by Lieutenant-Colonel David Semple, R.A.M.C., the Commission reached the conclusion that the contamination with tetanus bacilli was present in the vaccine before the bottle, 53N, was opened at Mulkowal. How it became contaminated they were not prepared to say. The three main possibilities they considered were: (a) the bottle may have been insufficiently sterilized before it was filled; (b) the decanting may have been performed with defective precautions; (c) the final sterilization may have loosened the stopper with the result that the specific contamination entered, either in the cold bath, or afterwards before the bottle was opened at Mulkowal.

Experimental work by Semple had shown that tetanus bacilli, when planted in a bottle of water-agar vaccine to which 0.5 per cent carbolic acid had been added, failed to grow, whereas in vaccine to which no carbolic acid was added they grew freely. The Commission therefore regarded the omission of carbolic acid from the vaccine as a grave mistake. Martin at the Lister Institute agreed with this, but made a reservation that 0.5 per cent carbolic acid might be inadequate to control bacterial growth in the presence of gross contamination.

Review of the evidence

Looking back on the evidence sixty years later I am in agreement with the main conclusion of the Commission, namely that the contamination of the vaccine with tetanus bacilli took place before the bottle, 53N, was opened at Mulkowal; but I think that it is possible to go a little further than the Commission was prepared to do in suggesting how the contamination occurred. Before entering on this, however, it may be as well to state the reasons why contamination after the bottle had been opened could not have explained all the facts.

The belief that this did occur was, of course, held by Haffkine himself, and also by Gibson and, to some extent, by Surveyor, and was strongly supported later on by Simpson (1907). The main grounds for their contention were that: (a) according to Major Elliot, who claimed to have an acute sense of smell, the bottle smelt perfectly normal when it was opened, and according to Lieutenant-Colonel Semple who examined the remains of the vaccine in the bottle some days later at Kasauli, it had the characteristic smell of a tetanus culture; and (b) if tetanus bacilli had been growing in the bottle before it was opened at Mulkowal it would have contained toxin, and the incubation period of tetanus in those who were injected with it would have been shorter than 5-6 days.

The first contention would have more weight if Major Elliot had smelt the bottle under the same conditions as Lieutenant-Colonel Semple; but in fact he smelt it in the open air. Had the smell of tetanus bacilli been strong, he would undoubtedly have noticed it, but if only a weak growth had occurred, then in the aromatic air of an Indian village he might well have failed to perceive anything unusual. The second contention is a strong one if it is assumed that the tetanus bacilli had grown well in the bottle; but if only a weak growth had occurred, then an incubation period of 5-6 days is

just what would be expected. In the St Louis, Mo., incident of 1901 in which the diphtheria antiserum used contained tetanus toxin the children were all dead in 6 days. Admittedly children may be more susceptible than adults, but even so an incubation period of 5-6 days, as at Mulkowal, suggests that the vaccine cannot have contained very much toxin. On the other hand it is probable that if tetanus spores had gained access to the bottle at the time of opening the incubation period would have been considerably longer than it was, and the chances of all 19 persons injected with the contents of bottle 53N contracting fatal tetanus would be very small. The reason for this is that without gross contamination with earth—and of this there is no evidence—only a few tetanus spores could have entered the bottle, and all our experience goes to show that the introduction of a few toxin-free spores into healthy tissue in the absence of any necrotizing agent or foreign body would almost certainly not give rise to tetanus. The comparative absence of smell of the vaccine coupled with the incubation period of 5-6 days, which is longer than would be expected of a highly toxic culture of tetanus and shorter than that of tetanus following a wound, seem to me to point strongly in favour of the view that the vaccine was contaminated at some stage in its preparation, and that the tetanus spores introduced multiplied to only a small extent and formed only a small amount of toxin. The toxin, however, would be sufficient to enable the spores to germinate in the tissues and thus lead to a shortening of the normal incubation period.

The possibility that the vaccine itself was not contaminated either before or after the opening of the bottle, but that the contamination entered by way of the syringe or needle, is open not only to the same objections as those just raised against contamination of the bottle after opening, but to the objection that the chances of nineteen persons in succession being infected with approximately the same number of tetanus bacilli as to result in their all contracting tetanus after almost identically the same incubation period would seem to be remote. Moreover, if the syringe was infected, why were the cases of tetanus restricted to the recipients of the vaccine in the single bottle, 53N?

If, then, it is agreed that the vaccine was contaminated during the course of preparation, how, it may be asked, did the contamination occur? There are two pieces of information in the report to which, quite understandably, no special significance was attached at the time. The first is that the tube through which the bacillary suspension was decanted ran through a fitting made of plaster of Paris. Dr Surveyor, who was the only one to mention this, remarked that the fitting would sometimes get cracked and allow any organisms on its under surface to contaminate the vaccine—presumably by falling into the bottle around the tube. It was not realized at the time that plaster of Paris might contain tetanus spores (Murray and Denton 1949), and might, therefore, constitute the source of contamination of the vaccine.

The second is that the bacillary suspension was not filtered and, therefore, almost certainly contained multiple small particles of agar. These would serve as a nidus for the growth of tetanus bacilli in the bottle and again after their introduction into the tissues.

My tentative conclusion, therefore, is that the vaccine in bottle 53N became contaminated when it was being filled, possibly by contaminated particles of plaster of Paris falling into it around the tube through which the vaccine was delivered; that the tetanus spores germinated inside the small agar particles present in the unfiltered vaccine; that between the latter half of September, when the vaccine was prepared, and the end of

October, when it was used, the resulting tetanus bacilli multiplied to a moderate extent and formed a small amount of toxin; that when the vaccine was injected into the tissues the Eh was lowered sufficiently by the presence of the toxin and the agar particles to enable further growth and toxin production to occur; and that the newly formed toxin, together with that already present in the vaccine, led to the development of tetanus in a shorter time than would have been expected if toxin-free spores had been introduced.

So far as I can see, the only objection that can be raised to this explanation is that the bottle, 53N, was one of five that had been filled at the same time from a single flask of bacillary suspension, and was the only one that gave rise to trouble. The other four were used without ill effect. It must be presumed therefore that the tetanus contamination was confined to one bottle, or that the other four bottles, though contaminated, were stored and transported in such a way as to be unfavourable for the growth of tetanus bacilli.

In view of the evidence given to the Commission of the way in which the decanting was carried out and of the technical unsuitability of the staff responsible for its operation, the first alternative seems to be the more likely. Dr Surveyor, who was a colleague of Haffkine's and had worked with him off and on for six years, but who was not in the Parel laboratory at the time the 53N brew was prepared, said that, on rejoining the laboratory shortly afterwards, he formed the opinion that the subordinate staff was not up to the mark and ought not to be employed. 'In the decanting department they had to make cultures for testing the flask and to decant cultures still alive; decanting from agar is much more difficult than decanting broth; agar gets into the syphon and there was a pump to drive it out or suck it in I never used. The flask had to be frequently shaken and the syphon handled and in a room with germs this involved additional risk.' 'The staff was certainly not qualified to carry out the work safely: it was most dangerous.' Added to this, it may be mentioned that the decanting of the suspension into five bottles labelled 53N was done by an assistant, called Stephen, who commenced practical work on that day for the first time. If the vaccine was contaminated by organisms becoming detached from the under surface of the plaster of Paris fitting through which the decanting tube passed, it is not difficult to understand how only one of five bottles might be affected in this way.

There is no question that the conditions in the laboratory were far from satisfactory, and that the subordinate staff were not properly trained to deal with the water-agar process that had replaced the simpler broth technique. Haffkine was under very heavy pressure to produce more vaccine, and he was undoubtedly doing his best with the unqualified assistants he had to help him; but the risks he ran were great and it is not surprising that catastrophe should follow sooner or later.

The Commission expressed the view that carbolic acid is a valuable agent in restraining the growth of tetanus bacilli and that its omission from the plague vaccine was a grave mistake. It is curious that so experienced a bacteriologist as Haffkine did not realize this. He did not seem to understand that an antiseptic which failed to destroy tetanus spores nevertheless performed a very useful function in preventing their growth. The danger of omitting an antiseptic from vaccines and sera was unfortunately not fully admitted until after the Bundaberg catastrophe of 1928 (see p. 77).

One last word. Since writing this, I have read the account of the Mulkowal disaster given by Waksman (1964) in his short biography of

Haffkine, in which he comes to the conclusion that the disaster was due, not to carelessness in the laboratory, but to a gross neglect of ordinary precautions in administration. I hope I am not maligning Waksman in doubting whether he has ever read the original evidence given in the Report of the Commission. His account seems to be compiled largely from annotations in the *Lancet* and *British Medical Journal* and from that given by Simpson, who was a close friend of Haffkine's. Had he studied the verbatim evidence, I doubt whether, while wishing to exonerate Haffkine, he would have come to the same conclusion.

Parish (1965), on the other hand, in his *History of Immunization* takes the view that the contamination probably occurred in the laboratory as a result of the lowering of standards that took place under the increasing demand for more vaccine.

The real question is not whether Haffkine was to blame, but how infection was introduced. To my mind the evidence in favour of the vaccine having been contaminated in the laboratory is so strong as to be almost conclusive.

CONTAMINATION WITH TETANUS BACILLI

Diphtheria antitoxin: Italy 1900

The brief account of this incident given by Siegert (1901) is amplified here by a certain amount of private information.

In December 1900, some children who were suffering from diphtheria were treated with an antitoxic serum prepared several months previously at the privately owned Serotherapeutic Institute of Milan and bottled in November 1900. Some of the children—at least eighteen—contracted tetanus after an incubation period of 6-9 days and thirteen of them died. The remainder apparently suffered from only a mild form of the disease and soon recovered. The exact number of children who were affected is not known, and may well have been greater than eighteen.

Altogether 305 bottles of the particular batch of antiserum concerned had been distributed; 230 were recalled, leaving a balance of 75, some and possibly all of which were used. Investigation showed that the serum responsible was a 'return serum', that is, one which had been issued and returned unused to the Institute. In its preparation 0.5 per cent phenol had been added. Examination after the accident showed that a bottle from the incriminated batch contained at least 0.32 per cent of phenol.

In all the bottles that had caused tetanus a sediment was observed in which abundant streptococci were visible microscopically, together with certain other organisms. Cultural and animal experiments revealed also the presence of tetanus bacilli, in numbers suggesting that they had multiplied along with streptococci in the therapeutic serum.

The bottles themselves were closed by corks—of what type is not known—and it was established that these corks were contaminated with tetanus bacilli.

This is all the information available. From it no definite conclusions about what actually happened can be drawn. There is no doubt that tetanus spores would survive for months in the presence of 0.5 per cent phenol, but why streptococci should survive and multiply is less obvious. Hazarding a guess, one would suggest that the corks were contaminated, not only with tetanus spores but with other organisms including streptococci, and that after insertion of the corks the bottles were not inverted or, after momentary inversion, were left upright for some time at a fairly high atmospheric temperature. Under these conditions, if the corks

were moist when inserted, the concentration of phenol in the layer of serum covering the under surface of the cork may have been too low to prevent the growth of contaminating aerobic organisms in contact with it, and these may have lowered the oxygen content of the bottle sufficiently to permit the germination of tetanus spores.

This explanation would account for a limited growth of aerobic and anaerobic bacilli in contact with the cork. It is difficult on the face of it to see how it could account for the heavy microbial sediment that was stated to be present in all the incriminated bottles, rendering it evident that the organisms must have been multiplying in the serum itself. Two factors, however, have to be taken into consideration. In the first place the concentration of phenol added to the serum may have been less than 0.5 per cent. Indeed, in the only bottle examined, it was found to be not more than 0.32 per cent. Phenol is a disinfectant with a high concentration coefficient. It has been calculated that doubling the concentration of phenol increases the reaction velocity 64 times, and that conversely halving it prolongs the reaction velocity by this amount (see Wilson and Miles 1955). Chick (1908) found that in an aqueous solution of 0.5 per cent phenol at 20°C paratyphoid bacilli were killed in 690 minutes. If the concentration coefficient, *n,* is taken as 6, this means that in the presence of 0.32 per cent phenol the organisms would not be completely destroyed for nearly a week.

Secondly, it must be remembered that in the Italian episode the phenol was present not in aqueous solution but in serum. Serum would have the double effect of neutralizing part of the phenol and of providing an excellent culture medium for the contaminating organisms.

It seems, therefore, not unreasonable to suppose that the effective concentration of phenol in the serum was too low to prevent the growth of streptococci and that these organisms rendered the conditions sufficiently anaerobic to permit the growth of tetanus bacilli, with the consequent production of tetanus toxin.

Smallpox vaccine: tetanus

This is a rare complication. In 1902, Willson, in the United States, recorded the history of 52 cases occurring throughout the world between 1839 and 1901. It is doubtful whether all these cases were genuine. In two cases, for example, convulsions, diagnosed as due to tetanus, came on within a few hours of vaccination. In most of the cases, however, trismus was specifically mentioned and was probably interpreted correctly as a sign of tetanus. Seven of the cases occurred in the years before tetanus was recognized as an infective disease, and for some time after this there were a few cases, mainly in England where humanized virus was still used for vaccination; but the majority of the cases were vaccinated with lymph of bovine origin. What was most striking was the length of the incubation period. In 50 cases in which information was available, the incubation period was as follows:

14 days or more	44 cases
20 days or more	31 cases
25 days or more	6 cases
28 days	1 case
7 weeks	1 case
8 months	1 case

That is to say it was generally between 2 and 4 weeks—considerably longer than the usual period observed in traumatic tetanus. The case fatality rate in the whole series was 78.8 per cent.

The same year McFarland (1902), also in the United States, collected a series of 95 cases occurring between 1854 and 1902. This series probably included a few of the 52 cases in Willson's series. Fourteen of them were published cases; the remaining 81 were collected by means of personal correspondence. Of the 95 patients, 61 died and 24 recovered; the fate of the remaining 10 was not known. The outstanding feature of this series was that 63 of the 95 cases occurred in 1901, most of them in the last three months of the year. They were grouped mainly in Philadelphia, Pa., Camden, N.J., Atlantic City, N.J., and Cleveland, Ohio. In 40 of these cases in which information was available seven brands of vaccine had been used. Those labelled A, D and F were all from equally large manufacturers; yet 30 of the 40 cases had been vaccinated with brand E. The incubation period of the cases ranged from 6 to 39 days, with an average of 22 days, similar to that in Willson's series.

Since 1902 comparatively few cases of tetanus after vaccination appear to have been recorded. This, of course, does not mean that tetanus has not occurred. There is a natural hesitation among doctors to publish an account of mishaps to their patients; and the risk of bringing vaccination into disrepute is a further, though possibly subsidiary, cause of their reluctance. Nevertheless any serious outbreak, such as occurred in the eastern part of the United States in 1901, would almost certainly have come to light, at any rate in the more developed countries of the world.

Among the few records that are available may be mentioned forty-one cases occurring since 1904 in the United States (Anderson 1915); two cases in Illinois (Report 1915); ten cases treated in the John Sealy Hospital at Galveston, Texas, between 1905 and 1938 (Moore and Singleton 1939); a few cases in Great Britain mentioned by Fildes (1929); thirty-four cases between 1951 and 1959, treated in the Medical College Hospital, Nagpur, by Bhatt and Anwikar (1962); twenty cases admitted to the King Edward Memorial Hospital, Bombay, during the four years November 1954 to October 1958 (Patel and Mehta 1963); and four in the hospital service of Gwalior (Laha and Vaishya 1965). In addition there are scattered cases described in the Italian literature; and a number of cases in the United States coming on after vaccination with the product of a single manufacturer and referred to by McCoy and Bengtson (1918), though without any information as to their exact time or location.

What was the mechanism responsible for the cases of tetanus that are on record and, in particular, for the extraordinary series that occurred in the autumn of 1901? Opinions expressed at the time varied. After the occurrence of eleven cases in Camden, N.J., in October and November 1901, the Camden Board of Health set up a special committee of inquiry. Their report was published in the *St Paul Medical Journal* issued on 29 November 1901 and was abstracted in the *British Medical Journal* (Report 1902). The Committee had samples taken of all the different brands of vaccine used at the time and submitted for examination to the laboratory. In none of them were tetanus bacilli found. Because of this negative result, and because of the unusually long incubation period of the cases—3 to 4 weeks—the Committee concluded that the tetanus bacilli were derived not from the lymph but from atmospheric contamination. At the relevant time there had been a long period of dry weather and high winds, and it was thought that the tetanus bacilli in the dust had gained access to the unprotected vaccination lesions.

The same conclusion was reached by Willson (1902). Both in cultural and animal inoculation tests he failed to find tetanus bacilli in any of the vaccine lymphs examined. He, therefore, concluded, as the Committee had done, that the vaccination lesions had become secondarily infected with tetanus bacilli present on the skin of the patient or carried to it by dust. He pointed out that many of the cases had been in children in whom the vaccination site was grossly dirty or was subject to obvious contamination.

A different view was expressed by McFarland (1902), who was influenced by the extraordinary outburst of cases in New Jersey and Philadelphia in the autumn of 1901, and by the fact that about 75 per cent of the cases had been vaccinated with the product of a single manufacturer. It was clear to him that some quite unusual circumstance had been responsible, and he was forced to conclude that the tetanus bacilli must have been present in the vaccine, though probably in numbers too small to be detected by the laboratory. He admitted that the long incubation period was a weak point in his argument, but explained it on the ground that the vaccinal lesion did not become favourable for the growth of tetanus bacilli for about a fortnight when crusts were beginning to form. He noted that in nearly every case the vaccination had taken well and a large lesion had resulted, presumably conducing to the development of anaerobic conditions. (Incidentally, McFarland, in the footnote to his article, says that Willson, in the paper he read to the Philadelphia Medical Society on 23 April 1902, which was published in the *Journal of the American Medical Association,* stated that he had discovered tetanus bacilli in vaccine lymph used at the time of the 1901 outbreak. On what ground McFarland based this information is a complete puzzle. There is nothing to this effect in Willson's own article, and the whole of Willson's argument is against primary infection of the lymph.)

The probable truth of McFarland's conclusion is supported by the finding of tetanus bacilli in vaccine lymph two years later by Carini (1904) in Switzerland. Examination was made of over 400 samples taken from 50 separate batches of calf lymph of Swiss and foreign origin, and tetanus bacilli were found, though in very small numbers, in 5 of the samples. The contaminated batches had been used for the vaccination of several thousand persons without any known ill effect. Carini considered that tetanus bacilli should be regarded as normal constituents of calf lymph. He advised that vaccination should always be superficial, avoiding piercing of the skin, and that occlusive dressings, which promoted anaerobic conditions, should be strictly avoided.

In the United States, Francis (1914) reported that, during the previous twelve years, in which the Hygienic Laboratory of the Public Health Service had examined vaccine virus received under the greatest variety of conditions and from many sources, not a single sample had been shown to contain tetanus bacilli.

McCoy and Bengtson (1918), who carried out an extensive investigation after the occurrence of a number of cases of tetanus following vaccination in which the product of a single manufacturer had been used, likewise failed to find tetanus bacilli in any of the lymphs examined, though they did show that the 'ivory' points used for vaccination, both before and after 'sterilization', were not uncommonly contaminated with these organisms.

In 1915 Anderson reported that he had studied 41 cases of post-vaccinal tetanus in the United States and had been unable to find tetanus spores in vaccine from the same stock as that used for the patients in question. He made a special examination of bulk vaccine lymph equivalent

to 200 000 doses and again failed to demonstrate the presence of tetanus spores. Finally he vaccinated rhesus monkeys and guinea-pigs with a mixture containing virus and abundant tetanus spores, and was unsuccessful in producing a single case of tetanus, even though the spores were sometimes demonstrable in the vaccine crusts. Anderson concluded that vaccine virus on the market did not contain tetanus spores; and that post-vaccinal tetanus depended on accidental infection of the wound at the time of crust formation.

Many years later Armstrong (1927), who was apparently unaware of Carini's paper, confirmed Francis's experience that extensive tests at the US Hygienic Laboratory had failed to demonstrate tetanus bacilli in vaccine lymph. He did mention, however, that he (1925) had demonstrated them in bunion pads, which were occasionally used as dressings for vaccination lesions. Analysis of the cases of tetanus after vaccination in the USA showed that all of them had followed primary takes, mostly after a large insertion, and that the vaccination site had been covered during a part or the whole of the time with a shield or dressing strapped to the arm. The resulting take was severe, leading to the development of a large ulcer or scar.

According to Armstrong, an occlusive shield constricts the blood vessels, and leads to stasis of the blood and lymph, to softening of the vaccine vesicle, and to exudation of serum and pus in which proteolytic organisms flourish and in which anaerobic conditions are established. The vaccine lesion spreads to the margin of the shield producing a large ulcerated area, sometimes containing portions of the gauze dressing that have become embedded in it and remained as a foreign body. Experiments carried out on monkeys and rabbits, which were vaccinated on the skin with a mixture of virus and tetanus bacilli, showed that a high proportion of animals in which a shield was strapped to the skin died of tetanus, whereas only one animal in which the inoculation site was left uncovered did so. Armstrong, therefore, formed the opinion that tetanus after vaccination was due to secondary infection of the wound with tetanus bacilli which multiplied under the anaerobic conditions provided by an occlusive dressing. Like McFarland (1902) he attributed the long incubation period to the inability of the tetanus bacilli to develop till the local conditions became propitious, about the 10th to the 14th day.

Armstrong's explanation may well fit a number of the sporadic cases of tetanus that have occurred after vaccination, but it is stretching the imagination too far to believe that it could apply to the outburst of cases in the United States in 1901. Something quite unusual must have happened in these circumstances, and far and away the most probable cause was contamination of the lymph itself. Owing to the occurrence of smallpox at the time, there was a big demand for lymph, and there is some reason to believe that insufficient precautions in its preparation had been taken by the manufacturer whose product was associated with most of the cases. There is no evidence that the use of a shield for covering the wound was specially prevalent at the time; indeed Willson's case histories do not support Armstrong's assertion that in all the American cases a shield had been used.

The completely negative results recorded by Francis (1914), by Anderson (1915), by McCoy and Bengtson (1918) and by Armstrong (1927) are undoubtedly very impressive and must be weighed against the five positive results recorded by Carini (1904). Some doubt, however, may be expressed as to whether the anaerobic technique and method of

attempted isolation used by the American workers were altogether suitable for the purpose.

In this regard it is of interest to note that Fildes (1929), who had made a special study of the growth requirements of the tetanus bacillus, records that he isolated a toxigenic strain of this organism from the only specimen of lymph he ever examined.

In summary it may be concluded that post-vaccinal tetanus is a comparatively rare occurrence. In spite of the tens of millions of vaccinations that have been made during the last century and a half, records are available, at most, of only a few hundred cases. The cause is probably twofold. Either the lymph itself is contaminated with tetanus bacilli, or the vaccine wound becomes secondarily infected, directly or indirectly from dust. The second explanation probably accounts for most of the sporadic cases, but the occurrence of groups of cases at the same time must almost certainly be attributed to primary infection from the lymph. In either case the local conditions must be such as to favour the development of the bacilli. The mere presence of tetanus bacilli in the vaccine wound, whether derived from the lymph or from dust, is not enough. Anaerobic conditions are required, and these do not seem to be present till the lesion begins to crust, towards the end of the second week, so that the incubation period is longer than it usually is in traumatic tetanus. It is highly probable that the establishment of the requisite conditions is promoted by the use of a shield or other form of occlusive dressing, but heavy secondary infection with aerobic organisms or the presence of a foreign body in the wound may have the same effect.

During the years that have elapsed since the outburst of cases in the United States in 1901, and again in the early part of the first world war, the preparation of vaccine lymph has undergone progressive improvement, and it seems unlikely that the conditions which led to the contamination of the vaccine then will recur. The greater care taken over the operation of vaccination itself and the subsequent treatment of the lesion also help to explain the practical absence of tetanus in Europe and America, as a complication, during the last fifty years or so. Perusal of the older literature reveals the appalling amount of sepsis that characterized so many of the vaccination sites; and indicates how rare it is for tetanus to occur after superficial lesions, to which the bacilli must frequently have gained access from soil, manure and dust.

CONTAMINATION WITH TUBERCLE BACILLI

Measles antiserum: Vienna 1922-3

In a hospital in Vienna 25 children were injected prophylactically with a batch of convalescent measles serum that had been drawn from three von Pirquet positive subjects. Two to three months later three of these children suffered from a swelling at the site of injection and of the inguinal glands. In two of the children the skin at the local site had ulcerated. Examination showed the presence of tubercle bacilli that were virulent to guinea-pigs. All three children had become highly sensitive to tuberculin. Kundratitz (1924), who records this episode, concludes that the tubercle bacilli must have come from one of the blood donors. The fact that only three of the 25 children suffered from inoculation tuberculosis suggests that the number of tubercle bacilli in the circulating blood must have been small. Kundratitz recommends that measles serum should be taken from only tuberculin-negative subjects.

The explanation given by Kundratitz, namely that the tubercle bacilli were derived from the blood of one of the donors, may be correct, but in view of the infrequency of tuberculous bacillaemia in apparently healthy tuberculous subjects (Wilson 1933) it seems more probable that the organisms gained access to the serum by a contaminated syringe, as in so many other similar incidents (p. 123).

CONTAMINATION WITH *Treponema pallidum*

Human vaccine lymph

Calf lymph for vaccination against smallpox did not become generally available till about 1870. Before then it was customary to use arm-to-arm vaccination with all its attendant hazards. Among these, syphilis was one of the most serious. Most cases transferred in this way were sporadic, but occasional outbreaks did occur. Smillie (1952), for example, related how in Rialta in Italy in 1861 no fewer than forty-six children and twenty nurses were infected with syphilis from a donor who formed the start of a series of arm-to-arm vaccinations.

BACTERIAL PYROGENS

According to Bennett and Beeson (1950), who reviewed the properties and effects of bacterial pyrogens, Billroth in 1865 noticed that the intravenous injection of saline into dogs was sometimes followed by a rise in temperature. Similar observations were made by other workers, and in 1876 Burdon Sanderson gave the name 'pyrogen' to a fever-producing substance prepared from putrid meat in which the bacteria were killed by alcohol. Wechselmann (1911) attributed the rigors, fever, diarrhoea, vomiting, cyanosis and headache that so often followed the intravenous injection of saline solutions of salvarsan to the action of bacteria in the distilled water. The toxicity of most samples could be removed by filtration through a kieselguhr candle or by autoclaving, but this was not successful with all samples.

Hort and Penfold (1911) then showed that freshly distilled water was non-toxic on intravenous injection into rabbits, but that water allowed to stand at room temperature for 48 hours or more produced high fever, even after boiling. As the pyrogenic property of the water could not be destroyed by autoclaving or by filtration through a Doulton candle, they concluded that it was due to a soluble bacterial product. Later Hort and Penfold (1912*a*) found that it could be removed by filtration through Martin's gelatin filter—suggesting that it was a colloid—and (Hort and Penfold 1912*b*) that it was destroyed at once by oxidation, as by hydrogen peroxide.

Jona (1916), who had been working at the Lister Institute along with Hort and Penfold, confirmed these findings and showed that as small a quantity of bacterial substance as 0.000 004 g of dried *E. coli* was sufficient to cause fever in a rabbit. He formed the opinion, based largely on Sebastiani's (1912) observations, that the pyrogenic substance was not a protein. Though Hort and Penfold (1912*a*) had suggested that the fever which follows the injection of various substances, including tissue extracts, was sometimes attributable to bacterial pyrogens in the solvent, it was generally believed that the fever caused by the intravenous injection of proteins was due to the protein itself; and it was referred to as protein shock.

Little further attention was paid to this subject till Seibert (1923) in the United States took it up again. Like Hort and Penfold, she found that a

febrile reaction occurred after the intravenous injection of rabbits with distilled water. She brought evidence that the pyrogenic substance was filtrable, heat-labile, non-volatile and non-dialysable, and was not present in all batches of distilled water. She (Seibert 1925) further showed that it could be removed by distillation; and that chills and fever in man could be produced by the intravenous injection of 80-100 ml of saline made from pyrogenic water but not from freshly distilled water.

The conclusion she reached in her earlier paper, that the pyrogenic substance was of bacterial origin, was confirmed by further work with Mendel (Seibert and Mendel 1923). These workers found that sterile proteins, such as that of fresh egg, or solutions of proteins prepared aseptically, caused no reaction; nor did proteins dissolved in alcohol which, of course, prevented bacterial growth. This led them to conclude that so-called protein fevers were due not to the protein itself but to the products of bacterial contamination.

The subject came very much to the fore when antiserum was introduced in the United States for the treatment of pneumonia. Large quantities of antiserum had to be injected—much larger than those necessary for the treatment of diphtheria—and the intravenous route was almost imperative. Felton (Felton and Kauffmann 1931), who was responsible for the preparation of a concentrated antibody solution, found that the pyrogenic reaction was associated with a protein that could be precipitated in a neutral salt solution at pH 4.8–5.2; and concluded, like Seibert, that the pyrogenic substance was formed as a result of bacterial activity during the processing of the antiserum.

Clinically the intravenous injection of a bacterial pyrogen in man is followed in 45-90 minutes by a rise in temperature along with a feeling of chilliness or by actual rigors, headache, pains in the back and limbs, malaise, nausea and leucopenia. The chill lasts 10–20 minutes. The fever reaches its height during the 2nd or 3rd hour and then diminishes rapidly to the accompaniment of profuse sweating, pupillary constriction, a polymorphonuclear leucocytosis and a fall in blood pressure. Very occasionally the thermal reaction may be so severe that the patient dies of hyperpyrexia (Cecil 1935, Kojis 1942). Pathologically, large doses in animals cause widespread capillary damage, which may, as in the Shwartzman phenomenon, lead to tissue necrosis.

Not all bacteria form pyrogens. Among the most active are the gram-negative bacilli, particularly those of the *Escherichia, Salmonella, Proteus, Serratia* and *Pseudomonas* groups. Chemical studies have shown that the responsible substance is a lipopolysaccharide of high molecular weight closely associated with the somatic antigen. Numerous workers extracted from *Salmonella typhi* an endotoxin that proved toxic to rabbits and mice in very small doses (see Morgan 1941); and Westphal, Lüderitz, Eichenberger and Keiderling (1952), using the method of Westphal, Lüderitz and Bister (1952) for extracting the somatic glycoprotein from *E. coli* with a warm 50 per cent solution of phenol in water, followed by repeated fractionation with ethanol to remove the nucleic acid and by ultracentrifugation, obtained a pure lipopolysaccharide that produced fever in man on intravenous injection in a dose of only 0.001i µg/kg. It may be remarked that the heat-lability attributed to the pyrogenic substance by Seibert (1923) was probably due to her working with an impure product still containing protein. The pure lipopolysaccharide is, of course, heat-stable.

The frequency of thermal reactions depends on the quality of the product and the quantity injected. Rutstein, Reed, Langmuir and Rogers

(1941), who studied the reactions of 2340 patients treated for pneumonia by the intravenous injection of antiserum, found that 18.4 per cent of them suffered from an early febrile reaction accompanied by a rigor.

Now that the cause of pyrogenic reactions is understood, manufacturers of serum products take precautions to minimize as far as possible bacterial growth at any stage of the processing, and little trouble need be expected in the future from pyrogens in antisera.

8

FAULTY PRODUCTION: VIRAL CONTAMINATION OF VACCINE OR ANTISERUM

THOUGH NUMEROUS bacterial diseases have been conveyed by contaminated prophylactic agents, the only viral disease transmitted in this way, of which we have any sound cognizance, is hepatitis.

This disease is essentially a human disease and has always been associated with the injection of human blood, plasma, or serum in some form or other. It has followed plain transfusion; the injection of convalescent plasma or serum for the prevention of measles or mumps; the use of normal serum for the preparation of yellow fever vaccine; the use of human lymph for vaccination against smallpox; and the injection of various prophylactic and therapeutic agents by a syringe contaminated with tissue juice from an infected patient in the manner described in Chapter 9 (p. 124).

There are two main forms of viral hepatitis—infectious hepatitis and serum hepatitis. These forms appear to be due to separate, though closely similar, viruses, but their relation to each other is still not clear. Infectious hepatitis may occasionally be transmitted by contaminated syringes or reagents, but most of the cases of hepatitis transmitted in this manner have been of the serum form.

Serum hepatitis is the same disease as homologous serum jaundice; transfusion jaundice; syringe jaundice; and the arsenic jaundice that used to be observed in patients treated for syphilis. It is caused by a virus, about 26 mμ. in diameter, which may be found circulating in the blood for several months before and sometimes for as long as five years after an attack. Infected serum may convey the disease in minute quantities; in some batches even 0.004 ml has proved infective.

There is no need here to enter into a fuller account of the disease or of the way in which it is transmitted (for references see Rhodes and van Rooyen 1958, Wilson and Miles 1964*c*). Suffice it to say that the injection of any form of fresh or dried human blood, plasma or serum carries with it a risk of hepatitis, though there are ways in which this risk may be minimized. Vaccines should never be made up with human serum; vaccine lymph for inoculation against smallpox should never be derived from human sources; and human serum for prophylactic or therapeutic use should always be administered in the form of gamma globulin prepared by a process that can be relied upon to destroy the virus.

With the very imperfect records at our disposal, it is dangerous to be dogmatic; but so far as the evidence goes it is probably true to say that more cases of serum hepatitis have been conveyed by inoculation than of any other disease. The reason for this is that its mode of spread by reagents and apparatus contaminated with human serum or tissue juice was not appreciated until quite recently, and that for long years before then thousands and thousands of persons had been infected by transfusion, by inoculation, by vaccination, by therapeutic drug treatment or in some other way with the virus of the disease. Now that its mode of transmission is understood, the incidence of the disease should be greatly diminished, though it is too much to hope yet for its complete elimination.

The following short accounts will afford some indication of the extent of the damage wrought by the virus. They concern only incidents in which the product to be injected was contaminated during its preparation. Incidents in which the product was contaminated not during preparation but by **a** syringe at the time of inoculation will be described in the next chapter.

Serum hepatitis after smallpox vaccination

The earliest record of post-vaccinal hepatitis appears to be that given by Lürman (1885) of an outbreak at Bremen in 1883-4; this outbreak is referred to by Hirsch (1886). The population affected consisted of the employees of the Actien-Gesellschaft Weser, a company that built ships and manufactured machinery and other iron goods. About 1200-1500 workers were employed at the time. Jaundice broke out in October 1883 and continued till April 1884, the maximum incidence being reached in December. All classes of worker were affected. Careful investigation seemed to relate the outbreak to vaccination.

Because of a few sporadic cases of smallpox among the employees, it was resolved to vaccinate or revaccinate the entire staff of the company. This was carried out on 13 August 1883 by six doctors working in three different parts of the factory. They used humanized vaccine lymph in glycerol supplied by a local chemist who had obtained it from elsewhere. It was delivered in four leaden containers each holding 100 tubes of lymph. Vaccination was performed by the scratch method. The lancets were cleaned between each inoculation with 1 per cent phenol solution. The distribution of jaundice cases was as follows:

Room A	141 out of 540 persons vaccinated
Room B	35 out of 466 persons vaccinated
Room C	14 out of 283 persons vaccinated

It was established that not all persons who contracted jaundice had been vaccinated with lymph from the same container. The figures showed that the attack rate was higher in men vaccinated in room A than in rooms B or C, suggesting that the lymph in the leaden container supplied to room A was more heavily infected with the hepatitis virus than in the containers supplied to the other two rooms. Fifty men who were absent on 13 August were inoculated, when they returned, with the remains of the vaccine; of these, only one contracted jaundice.

Corroborative evidence that the vaccine lymph was at fault was not lacking. Thus 87 members of the management who were vaccinated by their own private doctors with different lymphs all remained well; not a single case of jaundice occurred among them. Moreover about 500 men who were taken on to the staff between 13 August and April of the following year and who were apparently not vaccinated likewise remained free from the disease. There was thus no evidence that the disease was contagious.

Looking back with our present knowledge, there seems no doubt that the jaundice was a manifestation of serum hepatitis conveyed by an icterogenic virus present in the vaccine lymph.

Serum hepatitis after measles antiserum

In 1938 Propert reported the occurrence of hepatitis after the injection of 'convalescent' measles serum for the purpose of preventing measles in

contacts. Seven children in a mental institution were each given 4.5 ml of serum obtained from a reputable commercial firm. Within 78—83 days all children became jaundiced and severely ill. Three of them died of acute atrophy of the liver.

In the annual report of the chief medical officer of the Ministry of Health for 1937 (Report 1938) an account is given of a similar incident in which between 82 and 109 persons—the exact number was not known—were injected with 'convalescent' measles serum from a given batch. Of these, 37 contracted jaundice about 16 to 100 days later and seven died. Another incident occurred later after the injection of serum belonging to two small batches, but no details are given.

Some years later (Report 1943) unnamed medical officers of the Ministry of Health reviewed the subject of homologous serum jaundice. They referred to the incident in 1937 already described, but gave more exact figures, namely 41 out of 109 recipients of serum, eight deaths, and an incubation period of 16—114 days with a median of 71 days. In the fatal cases coffee-ground vomit and extreme physical restlessness were common, and the liver of four patients examined at postmortem showed widespread cellular atrophy.

A further incident was described by Cockburn and his colleagues in 1951. Seven out of ten persons receiving human plasma from the same batch for the prophylaxis of measles experienced a severe attack of hepatitis coming on 57 to 64 days later and three of the seven died. One of the fatal cases suffered from encephalitis without jaundice. The plasma came from a single batch collected from 60 donors, of whom six had a history of jaundice; none of these six, however, could be incriminated. From the same pool of plasma gamma globulin was prepared and used for measles prophylaxis. Only one out of 56 persons who received the globulin and were followed up suffered from jaundice—and that only a mild attack—suggesting that the processing had largely destroyed the virus.

Serum hepatitis after mumps convalescent serum

Beeson, Chesney and McFarlan (1944) described an outbreak of serum hepatitis among recruits in the British Army after injection with serum withdrawn from patients convalescent from mumps. Two lots of 'convalescent' serum were prepared, A and B. Lot A was given intravenously in a dose of 4-6 ml to 266 susceptible soldiers. Lot B was given intravenously just over a fortnight later in a dose of 8 ml to 204 of the same 266 men. Hepatitis developed 59-94 days later and affected 44.7 per cent of the 226 men who were followed up. No one received lot B only, but 17 cases occurred among those that received lot A only. It seemed therefore as if a hepatotoxic agent, which the authors regarded as different from the virus of infectious hepatitis, must have been present in lot A of plasma. This lot had been filtered and preserved with 1/2000 merthiolate, without removing or destroying the virus.

Serum hepatitis after yellow fever vaccine

The comparatively small number of cases of serum hepatitis reported after the use of human serum for the prophylaxis of measles or mumps is as nothing to the enormous number occurring after yellow fever vaccine.

Findlay and MacCallum (1937) drew attention to the icterogenic property of some batches of yellow fever vaccine. Among 2200 persons immunized against yellow fever during the preceding four and a half years

48 had had symptoms of hepatitis coming on 2—7 months after inoculation. The vaccine used was a 20 per cent suspension in normal human serum of mouse brain infected with the neurotropic strain of yellow fever virus. Both the serum and the vaccine had been filtered through a Seitz EK pad. Findlay and MacCallum were unable to offer a satisfactory explanation for the post-vaccinal jaundice, but they pointed out that, if it was due to a virus, the virus must be resistant to 0.2 per cent tricresol and 0.2 per cent ether.

A further paper by Findlay and MacCallum (1938) amplified the previous report, and stated that during the past five years 89 persons out of 3100 immunized against yellow fever had suffered from jaundice coming on 36 days to just under 7 months after vaccination. The last 1000 subjects had received a vaccine made with an attenuated strain of virus grown in tissue culture but injected with normal human serum. Even though latterly the serum had been heated to 56°C for 30 minutes, jaundice still occurred, namely in 13 out of 627 persons inoculated. Critically reviewing the evidence furnished by the cases they had seen, Findlay, MacCallum and Murgatroyd (1939) came to the conclusion that the infective agent present in yellow fever vaccine was a virus resident in the normal human serum with which the vaccine was prepared. This conclusion was amply confirmed later by American workers.

About the same time Soper and Smith (1938) reported on cases of delayed jaundice among persons injected with yellow fever vaccine in Brazil. Jaundice was observed in 20—30 per cent of persons injected with vaccines made up from two pools of serum from hyperimmunized monkeys, but not in any of 620 persons vaccinated with batches containing other pools of serum. The illness itself was fairly mild; half the patients had no fever; and none of the cases was fatal.

The use of yellow fever vaccine in South America was followed by further cases of jaundice in 1939 and 1940. Fox, Manso, Penna and Pará (1942) say that at the end of May 1939 vaccine lot 467 was used to inoculate 304 persons in the state of Rio de Janeiro. Jaundice was reported in October among 27 per cent of the vaccinated subjects. In another part of the state 8 out of 40 persons inoculated with the same vaccine were affected, and in Bolivia 6 per cent of 916 inoculated persons, making a total of about 140 cases.

The following year a still larger series of cases was observed among persons vaccinated at Espirito Santo in Brazil. Two lots of vaccine were incriminated. Lot 489 was used to vaccinate 9604 persons; of these, 736 suffered subsequently from jaundice and nineteen died. Lot 494 was used to vaccinate 9587 persons; of these, 150 suffered from jaundice and three died. The three batches—lots 467, 489 and 494—were the only ones out of 265 batches used that were definitely shown to cause jaundice, though there was a suspicion that some other batches were mildly icterogenic.

The incubation period in these cases ranged from 2 to 78 weeks, but most cases occurred between 12 and 20 weeks after inoculation. The vaccines had been made up with human serum, Seitz-filtered and heated at 56°C for 30 minutes. The authors came to no definite conclusions on the aetiology of the disease.

Large as these numbers were, they were dwarfed by the enormous number of cases that occurred in the American Army in the year 1942. At a press conference in Washington on 24 July 1942, the Secretary of War reported that 28 585 cases of jaundice had been observed in the Army between 1 January and 4 July after yellow fever vaccination, and of these 62 had proved fatal. No statement was made on the number of men

inoculated, but it was probably between 2 and 2½ million (Report 1942*a*). Death, when it occurred, was usually 2-6 weeks after the onset of the disease. Post-mortem examination revealed acute or subacute yellow or red atrophy of the liver. The conclusion was reached that the icterogenic agent was present in the normal human serum which had been used as a stabilizing agent in the preparation of the vaccine. The disease was non-infectious and did not spread to contacts (Report 1942*b*). After serum was omitted from the vaccine, cases ceased to occur.

Useful information on the aetiology of the disease was obtained from a study made after an outbreak of jaundice in the Virgin Islands in 1942. Lot 331 of yellow fever vaccine containing pooled human serum was used to inoculate 11 358 persons; about 500 cases of jaundice followed after 75 to 130 days. Samples of the vaccine and of serum from jaundiced patients were shipped to the United States, where they were inoculated into human volunteers in an institution. Thirty cases of jaundice were observed, coming on 4–19 weeks later. Attempts to transmit the disease to animals proved a failure. Evidence was obtained, however, to show that the icterogenic agent was filtrable, survived drying *in vacuo,* survived for a long time in serum stored at 4°C, and survived heating at 56°C for 30 minutes in the dried state. It was found, moreover, to be present in the blood before jaundice appeared, but not two and a half months after the jaundice had disappeared. In yellow fever vaccine it was destroyed by ultraviolet irradiation in one hour (Oliphant, Gilliam and Larson 1943).

Further cases were reported by Findlay and Martin (1943), who were successful in transmitting the disease to human volunteers by intranasal instillation of nasal washings taken from patients that had suffered from hepatitis after being injected with yellow fever vaccine.

Since the general omission of human serum from yellow fever vaccine, cases of hepatitis transmitted in this way have ceased to occur.

9

FAULTY ADMINISTRATION: USE OF NON-STERILE APPARATUS

CONTAMINATION OF a sterile product may occur before injection from contaminated apparatus or reagents; and contamination of the injection wound itself may occur from organisms naturally present on the patient's skin or deposited on it by contaminated cotton-wool or other material used for cleansing it.

It is convenient to divide faulty administration into two groups: one in which contamination is derived from primarily non-sterile apparatus, and one in which the apparatus is contaminated at the time of injection from the operator or his assistants. In this chapter we shall deal with the first group, making it clear, however, that the information available is not always sufficient to enable one to distinguish between the two modes of infection.

CONTAMINATED SYRINGE

Charolles 1932: local abscess formation

The available information about this incident is meagre.

On the 19th or 20th December 1932, diphtheria anatoxin was used for the subcutaneous injection of 172 children at Bourbon Lancy in the arrondissement of Charolles in the Département of the Saône-et-Loire. On the following day eight of the children were ill with high fever, headache, vomiting, and pain at the site of injection. One of them, who was ill beforehand and ought never to have been injected, died that day. The others recovered after a few days, but suffered from local abscesses that had to be opened and drained.

Inquiry showed that the anatoxin used came from the Pasteur Institute at Paris and was part of a batch that had been used uneventfully for the injection of several thousand other children. The injections themselves had been made by three doctors at Bourbon Lancy. The eight children that became ill had all been injected by one of these three doctors.

It seems probable that this doctor had used a contaminated syringe and had infected some of the children he injected. What organism was responsible for the abscesses is not clear, but presumably it was a staphylococcus or a streptococcus.

Ring, Co. Waterford, 1936: Tuberculous abscess formation

The incident at Ring in Southern Ireland in which 24 children injected with diphtheria prophylactic, TAF, suffered from inoculation tuberculosis and in which one of them died aroused a great deal of interest and was the subject of a lawsuit.

In 1936, Dr D. T. McCarthy, who was medical officer to two schools in County Waterford, namely the Friary School (St Augustine's College) and the Ring Irish College, decided on the advice of the county medical officer of health, Dr Michael O'Farrell, to immunize the children against diphtheria. For this purpose he obtained from Dr O'Farrell four 25 ml bottles of toxoid-antitoxin floccules (TAF) on 27 October, two on 4 November, and four on 16 November. All the bottles were supplied by Messrs Burroughs Wellcome and Co.; they belonged to two different batches. On 9, 17, and 24 November, Dr McCarthy gave intramuscular

injections of 1 ml to 44 children at the Friary School and to 38 children at Ring College. On the last date one and a half bottles were used at Ring College; the remaining half-full bottle was taken back to his surgery and, when examined later, was found to be sterile.

Early in January 1937, a 12-year-old girl who had been injected at Ring College was found to have a local abscess, enlarged axillary glands, and to be suffering from a generalized illness. She got progressively worse and died on 20 April of miliary tuberculosis and acute thrombocytopaenic purpura. At post-mortem there were extensive miliary lesions, and tubercle bacilli were demonstrated in the lungs, liver, spleen, kidney, glands and a small cerebral nodule, though not in the ulcerated granulomatous lesion at the site of injection.

Besides this girl, 23 other children who had been injected at Ring College suffered from local tuberculous abscess formation together with tuberculosis of the regional lymphatic glands. All of them recovered, and the local lesions healed within about nine months. None of the children injected by Dr McCarthy at the Friary School suffered any ill effect.

At the coroner's inquest on the dead child held during April, May and June 1937, it was stated that the syringes had been boiled in an electric sterilizer at the nearby hospital at Dungarvan and sent to the college in a drum. It was argued that the bottle of TAF used had contained living tubercle bacilli; and the Irish jury attributed the death to this cause, thus throwing the whole onus of blame on to the manufacturers (Report 19370*a, b)*. The father of the dead child therefore brought an action for damages against the Wellcome Foundation Ltd, in respect of this girl and of her three brothers, all of whom had suffered from local tuberculous abscess formation. The action was heard in Dublin from 6 to 23 February 1939, before the President of the High Court and a jury (Report 1939). It was again stated that the syringes had been boiled in a sterilizer, and sent to the college in a drum. The drum was too large to fit into the hospital autoclave; it had therefore been wiped inside with ether and lined with a sterile towel. It was also revealed that it was customary to reuse soiled dressings after they had been soaked, laundered and sterilized. The prosecution maintained that the bottle labelled TAF sent out by the manufacturers was in fact a suspension of tubercle bacilli which had been substituted by negligence.

The defence pointed out, first of all, that such a substitution was grossly improbable, partly because diphtheria prophylactics and tubercle bacilli were handled in two separate buildings, and partly because they were put into different shaped and different sized bottles. Moreover, if the bottle in question had been a suspension of tubercle bacilli of the same opacity as that of TAF, that is to say having a content of 6000-9000 million organisms per ml, it would have had in it the equivalent of 1/200 Old Tuberculin. This would have caused a severe reaction in tuberculin-positive children; in fact no such reaction occurred.

The defence reported that the unused half-bottle of TAF used on 24 November 1936, and eight other bottles of the same batch, had been found sterile and innocuous on injection into guinea-pigs. Experiments had shown that tubercle bacilli in 0.5 per cent phenol—the concentration used for preserving TAF—were killed within seven days, and that tubercle bacilli inoculated artificially on to rubber caps before waxing died within the same period. Since the bottles used at Ring had been filled 75 and 135 days before use and had had their caps waxed 2-3 months before use, it was clear that, even if tubercle bacilli had gained access to the bottles on

the manufacturers' premises, they could not possibly have survived this length of time.

Further experiments had shown that a minute drop of tuberculous sputum on the outside of a needle or on the plunger of a syringe could contaminate the interior of a rubber-capped bottle. This was offered as a possible explanation of the mode of contamination of the TAF. Alternative explanations were that the syringe needle had struck a small cold abscess in one of the children and carried tubercle bacilli into the bottle; or that the syringe and needles in the drum had been contaminated from imperfectly sterilized dressings previously used on a tuberculous patient.

In which way the contamination occurred was never discovered, but the evidence for the defence was so strong that the jury reported that the bottle did not contain live tubercle bacilli instead of TAF, and the President accordingly gave judgment for the Wellcome Foundation with costs.

France 1942-50: tuberculous abscess formation

The Ring case at the time of its occurrence in 1936 appeared to be unique. Debré, however, and his collaborators (1951) collected from the literature 95 cases of primary inoculation tuberculosis following subcutaneous injection of a number of miscellaneous substances such as penicillin, streptomycin, testosterone, boiled milk, saline, antisera and vaccines. They observed one case themselves after an injection of mixed diphtheria-pertussis-tetanus vaccine.

Of the 95 collected cases, 58 suffered from the disease after diphtheria-tetanus vaccine. They were grouped in eight incidents that occurred in France during the years 1942 to 1950 as follows, the numerator representing the number of cases and the denominator the number of children injected.

Oct.-Nov.	1942	Commune	St G.	in the Seine-et-Oise	26/162	
Jan.-Feb.	1943	Commune	L F	in the Seine-et-Oise	2/ ?	(4 / 200)
Apr.-May	1943	Commune	LF	in the Seine-et-Oise	2 /?	(4 / 200)
Nov.-Dec.	1943	Commune	C	in Charente-Maritime	10/90	
Nov.	1946	Commune	G	in Mayenne	7/15	
May	1949	Commune	L	in Gironde	2/2	
	1950	Commune	Y	in Seine-etpoise	1/1	
Oct.	1950	Commune	E	in Haute-Marne	2/2	
					58/530	

Infection was almost certainly due to imperfect sterilization of syringes and needles contaminated with tuberculous material. In one of the incidents it was established that the syringes, which were used for various other purposes, were never sterilized by boiling. Experimental observations showed that in pus or blood tubercle bacilli required 3-5 minutes' boiling for their destruction.

The authors point out that inoculation tuberculosis has never been reported after intradermal injection—possibly because intradermal syringes are not used for other purposes.

Bulgaria: tuberculous abscess formation

Mihov (1959) recounts a clinical and epidemiological study of 152 cases of inoculation tuberculosis occurring in five outbreaks in Bulgaria. Sporadic cases were the result of using a badly sterilized or contaminated syringe. Outbreaks followed injection with a syringe that had been used

for aspirating a tuberculous abscess and then used for serial injections in healthy subjects. A primary focus appeared at the site of inoculation together with regional lymphadenitis. Unfortunately there is little information on the nature of the substances injected, and it is therefore impossible to say how many of the 152 cases were associated with the injection of vaccines or sera. Most of the injections appear to have been of penicillin.

Royal Navy 1944-7: hepatitis after TAB vaccine

Ellis (1955) reported that during 1944 to 1947 the number of cases of non-surgical jaundice in the Royal Navy coming on 11-40 days after injection with TAB was greater than that expected on chance alone. The same was true in 1945 of cases coming on between 41 and 70 days after injection. No such distribution occurred after smallpox vaccination.

These findings are a little difficult to interpret. The incubation period of 11-40 days is far more in accordance with that for infectious hepatitis than for serum- or syringe-transmitted hepatitis, which is usually somewhere between 60 and 160 days. The explanation offered by Ellis himself is that the virus of infectious hepatitis was transmitted by the injections.

U.S.A. 1945: hepatitis after tetanus toxoid

A much more convincing account of a syringe-transmitted outbreak of hepatitis is given by Capps, Sborov and Scheiffley (1948) in the United States. On 31 August 1945, no men of a Service detachment received an intramuscular injection of tetanus toxoid administered from eleven 10 ml syringes each containing ten doses. Towards the end of September several men were found to be suffering from hepatitis. Only 56 of the **no** men were available for examination but, of these, eleven were affected with the acute disease. The incubation period ranged from 16 to 38 days, suggestive of infectious rather than of serum hepatitis. Though the needles had been changed for each injection, the syringes had not. In fact, each of the eleven syringes had been used for the injection often men. The syringes presumably became infected from the tissues of some of the men and carried the virus over to those injected subsequently. The authors calculated that 5 per cent of the no men must have been carrying the virus in their blood.

Mode of contamination of syringes

Syringe-transmitted disease has received a great deal of attention and many papers have been published on it. Briefly Hughes (1946) by the use of red blood cells, Malmros, Wilander and Herner (1948) by the use of fluorescein, and Christol (1949) by the use of fluorescein and radioactive sodium showed that syringes when used for injection might be contaminated with tissue fluid from the patient.

The mechanism of this was elucidated by Hughes (1946) and by Evans and Spooner (1950). They found that during the withdrawal of the syringe after injection a negative pressure was created which resulted in the sucking-up of tissue fluid into the needle and contamination of the nozzle of the syringe. These observations rendered it necessary to point out that the use of a separate needle for each injection was not enough; a separate syringe was likewise essential.

It cannot be too strongly emphasized that, if syringe-transmitted disease is to be avoided, a sterile syringe and a sterile needle must be

provided for the injection of each individual patient. Alternatively some form of needleless injection apparatus may be used, though whether all of these are completely free from risk is still a little doubtful.

Sterilization of syringes and needles is best carried out by exposure to hot air for one hour at a temperature of 160°C in a properly designed oven in which the temperature is kept more or less uniform throughout by means of a fan; or in an autoclave at 120°C for 20 minutes. Liquid disinfectants and the hot-oil method are not sufficiently reliable for general use (Report 1962*c*).

Most syringe-transmitted jaundice has followed the injection of drugs such as salvarsan, penicillin and adrenaline and does not therefore come within the scope of the present work. Those who are interested in it might consult the monograph by Ruge (1931), papers by Sheehan (1944) and Salaman, King, Williams and Nicol (1944), and the Medical Research Council's Memorandum (Report 1962*c*).

CONTAMINATED DISTILLED WATER

China 1926: streptococcal infection after diphtheria TAM

According to a report by Tsen, Dzen and Chang (1927) from the National Epidemic Prevention Bureau at Peking, 89 persons were injected at a hospital in December 1926 with a diphtheria toxin-antitoxin mixture that had been diluted before use with three times its volume of distilled water. The doses ranged from 0.2 ml to 2 ml of the diluted product. Of the 89 subjects injected, 33 suffered subsequently from single or multiple abscesses of the arm; four had a mild general reaction; five died from 3 to 13 days after the injection; and 47 had no reaction. Pus from the abscesses contained haemolytic streptococci.

Examination of the batch of TAM used showed that it was not fatal to guinea-pigs in amounts of 5 ml. The material was sterile, and had been filled into bottles three months previously. As experiments showed that haemolytic streptococci inoculated into a bottle could not survive at ice-box temperature for more than eight days, it was considered highly improbable that the material, which contained 0.3 per cent tricresol, was contaminated during filling. Moreover, the undiluted material from the same batch was injected into seven persons in the hospital on the following day, and was used at three other hospitals without causing any untoward reaction.

There seems little doubt that, though the distilled water used for dilution of the vaccine was said to have been autoclaved, it was responsible for conveying the infection. It is of interest to note that there was scarlet fever in the hospital at the time.

CONTAMINATED COTTON-WOOL

Olds, Alberta, 1938: streptococcal infection after diphtheria FT

In this incident several children injected with diphtheria toxoid suffered from local abscesses caused by a haemolytic streptococcus, and one died.

At Waterside School, Olds, Alberta, 29 children aged 16 months to 12 years received their third injection, 1 ml of diphtheria toxoid, on 21 September 1938. Twelve of these children became ill within a few hours to five days after the injection. Abscess formation or cellulitis requiring surgical interference occurred at the local site, and bacteriological examination of the pus revealed the presence of haemolytic streptococci belonging to group A. One child died 11 days later of asphyxia under

general anaesthesia during the course of an operation for drainage of what appears to have been a metastatic abscess of the leg.

Investigation showed that the injections had been carried out in the school kitchen which, though well lighted, was heavily infested with flies. One 5 ml and one 1 ml syringe together with three or four needles had been boiled in the doctor's surgery beforehand. After boiling, the needles had been picked up by hand and placed inside the barrel of the 5 ml syringe. The two syringes had then been wrapped in a piece of non-sterile gauze and a clean towel and taken to the school in the doctor's bag. At the same time the doctor took with him a 1-foot length of absorbent cotton-wool pulled off an open roll that had been kept in his surgery; it was protected by some blue paper in which the roll had originally been wrapped.

During the actual injections each child's arm was rubbed by an assistant with a piece of the non-sterile cotton-wool that had been liberally soaked in alcohol contained in a non-sterile dish. The doctor cleansed his hands in alcohol without previous washing. The same 5 ml syringe without reboiling or disinfection of any kind was used for the 29 children. In between each injection the doctor wiped the needle with cotton-wool soaked in alcohol, the same swab being used several times in succession. Twice during the procedure a needle had to be discarded owing to bending or blockage and replaced by a fresh one. The 29 children, therefore, were injected with one or other of three needles. Altogether five 6 ml ampoules of diphtheria toxoid supplied by the Connaught Laboratories were used. One additional child that was injected separately with the 1 ml syringe suffered from no trouble afterwards.

Two independent investigators—Dr D. T. Fraser of the School of Hygiene and the Connaught Research Laboratories, Toronto, and Dr R. M. Shaw, Provincial Bacteriologist, Alberta—both reached the conclusion that the streptococcal infection was probably derived from the non-sterile cotton-wool which may have become contaminated from a septic case in the doctor's surgery. The doctor himself when examined some days later was not apparently carrying haemolytic streptococci in his throat or on his hands. No swab, however, seems to have been taken from his nose; nor does his assistant, who cleaned the arms beforehand, appear to have been examined. Observations in the laboratory showed that haemolytic streptococci mixed with serum, smeared over freshly sterilized cotton-wool and dried in the incubator and subsequently at room temperature, were not destroyed completely by exposure to 'rubbing alcohol' (95.12%) for a total of 19 minutes.

Why only 12 of the 29 children suffered from septic arms was explained by the investigators as being due partly to the fact that three of them were injected with a recently boiled needle, which was not wiped with cotton-wool, and that the remainder had had the arm wiped with a piece of cotton-wool that was not contaminated with streptococci. This sounds reasonable, since the 12 children whose arms became septic were among the first nineteen to be injected. By the time the twentieth was reached it is assumed that the contaminated part of the cotton-wool had been used up. It may be added that bacteriological examination showed the diphtheria toxoid itself to be sterile.

In reviewing this episode it is a little difficult to know where the streptococci came from. It may well be that part of the cotton-wool used for rubbing the arms and for wiping the needles in between successive injections was contaminated in the doctor's surgery. Alternatively the doctor may have been carrying streptococci in his nose, which would have

rendered him a dangerous disperser, or his assistant, who was not examined at all, may have been infected. Wherever they came from, however, it is clear that the organisms were not destroyed by alcohol. This is not surprising, since practically pure alcohol was used. This is known to have little disinfectant action when applied to dry materials such as cotton-wool or a practically dry surface such as the skin of the hands. At between 50 and 70 per cent concentration alcohol is an excellent disinfectant, but at Olds no water seems to have been added to it at all, and the alcohol that was used came into contact only with dry materials.

This incident merely serves to emphasize the importance of using not only a separate properly sterilized syringe and needle for each injection, but also sterile cotton-wool, gauze, forceps and disinfecting fluid.

10

FAULTY ADMINISTRATION: CONTAMINATION FROM OPERATOR

NUMEROUS EXAMPLES are on record, not only with diphtheria prophylactic but with other prophylactic and therapeutic reagents, in which infection has occurred at the site of inoculation with an organism carried by one of the persons responsible for the preparation or use of the syringes. Nasal carriers of streptococci are known to be more infectious than throat carriers, and it is not difficult to understand how the syringe, the needle, or the skin of the child can be contaminated from the nasal mucus or pharyngeal exudate of an infected person.

Birmingham 1935: streptococcal contamination from nurse

Allison (1938) reported one very clear instance of this affecting the nursing staff of a large hospital that were being immunized with TAF against diphtheria. Injections were carried out on three days. Six out of 40 nurses injected on the first day and six out of 30 on the third day, but none out of 36 on the second day suffered from local abscess formation accompanied by lymphangitis and high fever. Pus from all the abscesses contained *Streptococcus pyogenes* type 1.

Inquiry revealed that the sterilization of the syringes and needles had been faulty and that on the first and the third day Sister X who was responsible for preparing them had been on duty. She was found to harbour type 1 streptococci in her throat. Infection had presumably spread from her hands to a bowl of saline used to rinse out the syringes and needles. No streptococci were found in the throat of Sister Y who was on duty on the second day when no reactions occurred in the injected nurses.

Further British incidents 1935-43: streptococcal infection and inoculation tuberculosis

During the years 1935 to 1943 records at the Ministry of Health showed that five incidents of streptococcal infection, including the one just recorded by Allison (1938), comprising 148 cases, occurred in Great Britain after injection with toxoid-antitoxin floccules (TAF), alum-precipitated toxoid (APT) or toxoid-antitoxin mixtures (TAM), and one incident of inoculation tuberculosis affecting four children after APT. The *streptococcal incidents* may be listed as follows:

1936 **Kingstanding, Birmingham.** TAM was injected into children; 15 children suffered from local abscess formation and two from local induration only. *Str. pyogenes* was isolated from eight of the abscesses. An attendant nurse had a severe cold at the time of the injection.

1942 **Bassett.** One child of seven years died of streptococcal septicaemia five days after injection with APT. The septicaemia followed cellulitis of the arm starting at the site of injection.

1942-3 **Acton.** After injection with APT 33 children suffered from severe local reactions, 25 of which went on to abscess formation. *Str. pyogenes*

type 15 was isolated from six of the abscesses and from the throat of the doctor who made the injections. The APT was sterile.

1942 **Crompton U.D.** Of 129 children injected with TAF, 81 suffered from inflammation at the site of injection; in 80 of the 81 abscess formation occurred. *Str. pyogenes* was isolated from six of the abscesses examined. Infection probably occurred through contamination of the needles by the doctor who picked them from a bowl of water with his hands.

In addition to these, *local abscess formation* was recorded in one boy injected with APT at Ashton-under-Lyne in 1941 and in four children injected with APT at Leith in 1943. In none of these cases was the nature of the causative organism identified.

The incident of *primary inoculation tuberculosis* referred to occurred in Lanarkshire in 1943. Four children who had been injected with APT were affected. They suffered from axillary adenitis, and from the pus of one case tubercle bacilli were isolated.

Bristol 1964: streptococcal contamination of sterile disposable syringe

An account by Cayton and Morris (1966) of abscess formation after the use of DPT vaccine is of special interest because sterile disposable syringes were used at the clinic. Four children suffered from local abscesses caused by *Streptococcus pyogenes* type 12. At the clinic a large disposable plastic-ended hypodermic needle was pushed by hand into the bottle of vaccine through the rubber cap and left in position till the end of the session. Ten children were injected with vaccine from this bottle. A fresh plastic disposable sterile syringe was used for each child, the vaccine being withdrawn through the fixed needle and the syringe then being fitted with a new sterile needle.

Examination showed that the batch of vaccine from which this particular bottle had been drawn was sterile; moreover, it contained 0.013 per cent thiomersal, which killed small numbers of streptococci in less than a minute. A representative sample of the disposable syringes and needles likewise proved to be sterile. So also did the highly bactericidal biniodide solution used for wiping the vaccine cap and cleansing the skin of the patient. No streptococci were isolated from the cotton-wool swabs that had been prepared at the clinic by the nursing assistant. On the other hand *Streptococcus pyogenes* type 12 was isolated from the nose of the doctor, the throat of the nursing assistant, and the scissors used to open the syringe packs and to prepare cottonwool swabs for the application of the biniodide solution. The cultures were made one week after the injections. During the week previous to the injections the nursing assistant had been off work suffering from tonsillitis.

Laboratory experiments showed that it was easy for the junction between the fixed needle and the syringe which was inserted into it for withdrawing the vaccine to be contaminated from the fingers. Fluid accumulated at the junction and could find its way into the interior of the needle or the syringe and thus contaminate the inoculum. There seems little doubt that this is what happened.

Even sterile disposable syringes have got to be handled carefully and needles should always be fitted with sterile forceps. The practice of inserting a large needle into the vaccine bottle through which to withdraw successive portions of vaccine is to be deprecated, since the butt inevitably

becomes wet and open to contamination from the fingers or nasal spray of the operator.

Holbaek 1938: streptococcal contamination from nurse

In this incident a small proportion of children who had been vaccinated against diphtheria suffered from a streptococcal infection apparently derived from an attendant nurse. The information given here is taken from Madsen and Henningsen (1939), supplemented by private sources.

On 11 and 12 January 1938, purified alum-precipitated diphtheria toxoid was used to inject 2408 children in Holbaek—a small provincial town in Denmark. The injections were made at a number of different schools by a team of workers including twelve doctors, ten nurses and some assistants.

Within 8-12 hours 34 children, all injected at one school on the same day, were febrile and some were suffering from diarrhoea and vomiting. On the same or the next day 21 of them had a scarlatinal rash unaccompanied by a sore throat or raspberry tongue. At the site of injection there were redness, swelling and tenderness going on in 29 of the children to abscess formation. The abscesses were of long duration and required surgical intervention; the pus from 22 out of 25 of them yielded *Streptococcus pyogenes* type 11 on culture.

The batch of alum-precipitated toxoid used for the injections came from the State Serum Institute at Copenhagen and was found on investigation to be sterile. No one in the department in which the ampoules had been prepared was suffering from scarlet fever or had been in recent contact with the disease. Streptococci inoculated into the toxoid died within 24 hours at 37°C and within ten days at 20°C; at 3–4°C they diminished steadily but could still be recovered after six weeks.

The sterilization of the syringes used for the injections appeared to be satisfactory.

Cultures made ten days after the injections revealed no streptococci in the nasopharynx of the doctor concerned, but did show the presence of *Str. pyogenes* type II in the nose and throat of the nurse who had handled the instruments used at the school where the cases occurred. This type was a common cause at the time of scarlet fever in Denmark. It seems probable that the syringes were contaminated directly or indirectly from the nasal mucus of this nurse.

Japan 1946: tuberculous contamination from doctor

A remarkable incident occurred in Japan in 1946, reminiscent of the Ring incident of 1936 in Ireland (see p. 120), in which a number of children suffered from inoculation tuberculosis after injection. The incident is described by Tamura, Ogawa, Sagawa and Amano (1955).

In the Hyogo Prefecture 631 primary-school children were injected twice at a week's interval with TAB vaccine. Of this number no fewer than 102 subsequently suffered from inoculation tuberculosis. The reactions were characterized either by (a) swelling and induration at the site of injection; or (b) a subcutaneous lesion proximal to the site of injection, presumably in the path of the lymphatic vessels, and often extending into the underlying tissues; or (c) involvement of the regional lymphatic nodes. Most of the lesions appeared about a month after the injections, but some were delayed for 4-6 months, and one did not come up for 12 months. Spontaneous ulceration occurred locally or in the lymphatic nodes in some children, and surgical excision was occasionally required. In three children

bone and joint lesions developed, and in a few X-ray examination showed the presence of pulmonary tuberculosis. It was not possible, however, to determine whether these children had been infected naturally or by injection.

The tuberculin reaction became positive in the affected children, and tubercle bacilli of the human type were demonstrated in the lesions of 29 of the children.

The injections were given by a woman doctor and two nurses, so that some children were injected by the woman doctor once, some twice, and some not at all. The woman doctor was found afterwards to be an open case of pulmonary tuberculosis, and tubercle bacilli of human type were isolated from her sputum. The vaccine used for the injections could not be obtained for examination, but the probability is that infection occurred through contamination of the syringe by the hands or sputum of the woman doctor. There are now numerous instances on record to show that this mode of infection is possible with staphylococci, streptococci, and tubercle bacilli.

It is interesting to note that none of the 102 children who suffered from inoculation tuberculosis died. In the Ring incident only one fatal case occurred among the 24 that were infected. Tubercle bacilli in small numbers can apparently be injected subcutaneously without serious risk to life. Indeed at one time live virulent tubercle bacilli were used for purposes of vaccination in the United States (Webb and Williams 1911, Baldwin and Gardner 1921). The practice was soon abandoned on account of its potential danger, but so far as is known no fatal cases were reported.

The result of cutaneous inoculation to produce lupoid lesions (von Aichbergen 1937) or of subcutaneous injection is different from that of alimentary infection, as is shown by the Lübeck experience (see p. 66). In this, 72 out of 251 infants died who had been given by the mouth a supposedly BGG vaccine which in reality was a suspension of live virulent tubercle bacilli (Report 1935). Strict comparison, of course, is not possible, partly because in the Lübeck catastrophe the subjects were infants, not children, and partly because the dose was probably very much larger. Nevertheless the frequency of fatal non-pulmonary tuberculosis in young children caused by the drinking of infected cows' milk is sufficient to show that ingestion of tubercle bacilli by the mouth involves a risk to life as well as to disease (see Wilson 1942).

Japan 1948: tuberculous contamination from doctor and nurse

In 1948 another incident similar to that just recorded after TAB vaccine followed the use of pertussis vaccine (Oka and Sato 1963).

On the 25th and 29th November 209 infants aged 4-33 months were vaccinated against whooping-cough by subcutaneous injection in the upper arm. Of these, 62 subsequently suffered from inoculation tuberculosis. Illness came on within about 4 weeks, manifesting itself by fever, lassitude, irritability, chilliness, anorexia, loss of weight, and night sweats. Large ulcerating lesions developed at the site of injection with swelling and sometimes ulceration of the regional lymph glands. Tubercle bacilli were demonstrated locally in 40 of the 62 cases. Healing of the local lesions took several months, in some children as long as two years. Six children suffered from miliary tuberculosis, with or without meningitis, arthritis or gastro-enteritis and two died. Three other children had tuberculosis of the knee or hip joint; and 27 showed on X-ray miliary

lesions in the lungs or hilar shadows. In many of the children the spleen or liver was swollen.

Investigation revealed nothing wrong with the vials of vaccine used or with other vials of the same batch. The syringes had been sterilized by boiling. Both the doctor and the nurse, however, who gave the injections were suffering from open tuberculosis and had presumably contaminated the syringes.

11

ALLERGIC MANIFESTATIONS
LOCAL ALLERGY

Cyst formation

THE OCCURRENCE of sterile abscesses, or what some workers prefer to call cysts, is not uncommon after the injection of alum-precipitated diphtheria toxoid. They become evident 1 to 6 months after the injections. They are commoner in older than in younger subjects, after subcutaneous than after intramuscular injection, after 1 ml than after 0.5 ml quantities of prophylactic, and in schick-negative than in schick-positive persons. They appear to constitute an allergic reaction to diphtheria bacillus protein and to be an indication of immunity (Pappenheimer *et al.* 1950, Volk *et al.* 1954). They may presumably act as fixation abscesses (Edwards 1942), though the evidence for this is incomplete.

Similar reactions may follow the use of alum-precipitated pertussis vaccine. In the experience of Sako, Treuting, Witt and Nichamin (1945) 10 out of 6600 injections in one series and 27 out of 703 in another were followed by abscess formation. The abscesses were all sterile and disappeared in 1–2 months, either with or without spontaneous rupture. Abscess formation was ascribed to the introduction into the skin of a needle covered on the outside with vaccine. When a separate dry needle was used for each injection, more than 1000 injections were given without a single abscess. This observation, combined with the early appearance and disappearance of the abscess, suggests that the cause of abscess formation may be different with pertussis vaccine than with diphtheria toxoid. The fact that, with both vaccines, it is associated with the use of alum renders it doubtful whether an explanation based wholly on allergy or on chemical irritation can be accepted.

Cysts have also been reported after the use of adjuvant vaccines. Beebe, Simon and Vivona (1964), for example, observed cyst formation in 0.1 to 4.1 per cent of different groups of soldiers receiving influenza vaccine containing an adjuvant. In these cases the cyst formation was presumably due to the direct irritant effect of the adjuvant rather than to allergy. The vaccine, however, did contain a little penicillin, and this sensitized some of the subjects so that they suffered from urticaria after a subsequent dose of penicillin.

Tyrrell (1965) states that, though adjuvant vaccines containing oil and emulsiflers give rise to less immediate reaction than saline influenza vaccines, they are sometimes responsible for an unpleasant delayed reaction occurring after weeks or months in the form of a local nodule that may interfere with a man's working capacity for quite a long time.

The Arthus phenomenon

An exaggerated local response to the repeated introduction of a foreign protein into the tissues was described by Arthus (1903). Successive subcutaneous injections of horse serum into the same place led in rabbits to an increasing inflammatory reaction characterized at first by transient swelling and oedema, later by more persistent induration, and finally by localized necrosis. Subsequent workers have brought evidence to show that the Arthus phenomenon is an allergic manifestation resulting from the

union of circulating antibody with antigen in the tissues (see Humphrey and White 1964*a*).

The Arthus type of reaction has been reported infrequently in human beings after two or more injections of vaccines or sera. There is reason to believe, however, that it is very much more common than the few reports in the literature would suggest. One of the first to describe a case was Thaon (1912), who observed a local phlegmonous inflammation in a man injected with tetanus antiserum four years after a similar prophylactic dose. Gatewood and Baldwin (1927) described cases in which severe local tissue necrosis occurred in patients sensitized to horse serum by immunization with diphtheria toxin-antitoxin mixture and subsequently given diphtheria antitoxin therapeutically or submitted to a diagnostic schultz-charlton test for scarlet fever. In one patient large swellings formed on the arm and the thigh where the antiserum had been injected. When they were incised they were found to contain quantities of pus and necrotic tissue, partly derived from the muscle.

Kojis (1942), who reviewed the literature, found records of 12 cases that exhibited the Arthus reaction after serum treatment, ranging from local skin necrosis to massive gangrene. Minor reactions, however, of this type must be quite frequent, as judged by my own observations on patients undergoing vaccine therapy with staphylococci or given repeated doses of tetanus toxoid. After each successive injection the local reaction becomes more severe till at last the local pain and induration can no longer be tolerated.

12

ALLERGIC MANIFESTATIONS: SERUM SICKNESS

Serum sickness

THIS CHAPTER will be confined to a description of the febrile illness in man that follows the injection of a foreign—usually horse—serum. Though it would be logical to include in it serum neuritis and serum anaphylaxis, it is proposed to consider these two sequelae separately along with the nervous and anaphylactic disturbances that may attend vaccine treatment.

The toxicity of foreign serum to man and animals has been known for a long time. The earliest reference to the use of lamb's blood for human transfusion is said to be that by von Denis in 1667 (see Rosenau and Anderson 1906). The practice was found to be dangerous and was soon abandoned.

Uhlenhuth (1897) reviewed the literature, and made observations himself on the toxic death caused by the intravenous injection of foreign animal sera into rabbits and the necrotic inflammation caused by the injection of large quantities of serum into the subcutaneous tissues of the guinea-pig. It was, however, Lublinski (1894) who drew attention first of all to the peculiar febrile illness for which von Pirquet and Schick (1905) later suggested the name serum sickness.

A child suffering from nasal diphtheria was given three injections of antiserum. Ten days after the first injection the joints of the feet became red and swollen. Then succeeded a fairly widespread erythema multiforme, fever, and severe pains in the knee and elbow joints. Complete recovery occurred in about a week.

Almost at the same time Cnyrim (1894) described two cases—both in his medical assistants who were treated with diphtheria antiserum. Symptoms came on 6 and 8 days after injection, and consisted of fever, adenopathy, an itching urticarial rash, and pains in the joints and muscles. Gottstein (1896) reported that in a series of 420 cases of diphtheria treated with antiserum serum sickness occurred in 23.3 per cent. Both Hartung (1896) and Daut (1897) studied the disease and contributed to our knowledge of its incidence, incubation period, variety of rashes, and of individual differences in the sera injected.

Serum sickness is a disease peculiar to human beings. Children are affected more often than the aged (Longcope 1943). In their monograph on serum sickness von Pirquet and Schick (1905) describe the symptoms in some detail. They regard oedema, seen mainly on the face, and swelling of the regional lymphatic glands as almost constant features. Fever is nearly always present and so is a rash, generally urticarial. The rash appears first at the site of injection, and spreads to the rest of the body. It is symmetrically distributed and is intensely itchy. It may be succeeded by one or two further eruptions, of a different nature—simple erythema, scarlatiniform or morbilliform. Joint pains are not so common, but when they occur are severe and are not relieved by salicylates. The spleen may be swollen; there is a leucopenia due to a fall in the number of polymorphs; and occasionally a bloody diarrhoea occurs lasting several days. The mucous membranes are not affected, and there is no vomiting—

both useful differential points in diagnosis. The duration of the symptoms is seldom more than 1 to 4 days, but after a large injection of serum the illness may persist for 4 to 5 weeks and be attended by prostration and emaciation.

These findings were confirmed by Currie (1907) at Glasgow and Goodall (1907) in London, both of whom were able to study large numbers of cases. On occasion an exceptionally severe illness may be experienced, as in Eason and Carpenter's case, in which the reaction, starting on the 8th day, is accompanied by tachycardia, dyspnoea, cyanosis and collapse; but the disease is never fatal. Other manifestations have been reported. Blum and Pollet (1924), for example, give references to cases of epididymo-orchitis, generalized adenopathy, cardiac irregularity, and serous pleurisy which were ascribed to the injection of serum; and McManus and Lawlor (1950) mention myocardial infarction as a rare complication. Perceptive deafness has also been reported (Pantazopoulos 1965).

The incidence of serum sickness varies with a number of factors, notably the reactivity of the patient, the quantity of serum injected, and previous experience of serum treatment. In Currie's (1907) series of 607 patients treated with diphtheria or plague antiserum, 339 (55.8%) suffered from a rash coming on most commonly on the 8th to the 10th day after the first injection. Weaver (1909) in his series of 692 patients treated with diphtheria antiserum observed serum sickness in 236 (34.1 %). The incidence ranged from 10.9 per cent in those receiving 1–9 ml to 80 per cent in those receiving 150 ml or more. The incubation period was commonly 6–10 days, and was dependent on both the number of injections and the quantity of serum injected. The importance of the quantity of serum administered was emphasized by Mackenzie and Hanger (1930), whose experience showed that in 100 consecutive patients given 100 to 1000 ml of pneumococcal antiserum 93 per cent suffered from serum disease.

Reactions are likewise said to be frequent after rabies antiserum, probably because the horse serum is not digested with pepsin and hence contains more foreign protein than refined serum, and because of the comparatively large dose—20 to 30 ml for an adult—in which it is injected. Karliner and Belaval (1965) reported an incidence of 16.3 per cent among 526 patients given rabies antiserum. It rose with age from 12.3 per cent in the 0–5 age group to 46.3 per cent in patients over 15 years.

Kojis (1942), whose patients were treated with antiserum against diphtheria or scarlet fever, had a much lower incidence of serum sickness—1264/11 211 or 11.3 per cent—possibly because of a lower dosage and the use presumably of partly purified serum. With enzyme-refined serum Laurent and Parish (1952) put the incidence as low as 5 per cent. Antiserum freshly withdrawn from the horse is said to be more toxic than after storage (Bujwid 1897).

The description of the disease given so far refers to that seen in patients given serum for the first time. It had early been noticed by Theobald Smith (see Otto 1909) that guinea-pigs receiving widely spaced injections of toxin-antitoxin mixtures became abnormally sensitive to further injections. He communicated his observations to Ehrlich in 1904, and Otto (1905) made a detailed study of what is sometimes referred to as the Theobald Smith phenomenon. Both Otto in Germany and Rosenau and Anderson (1906, 1907) in the United States showed that the injection of horse serum into a guinea-pig gave rise after an incubation period of not less than 10 days to a state of hypersensitiveness in which a further dose of

serum was liable to be followed within a few minutes to half an hour by an acute and often fatal reaction (see p. 209).

Man is very much less sensitive than the guinea-pig, and the chief effect of sensitization is to shorten the incubation period of serum sickness provided the second injection of serum is given not less than 10 days after the first, von Pirquet and Schick (1905) recognized an immediate reaction coming on within 24 hours of reinjection, and an accelerated reaction coming on 5-7 days after reinjection. Sometimes an accelerated reaction may follow an immediate reaction. The patient who has once been injected with serum, no matter how long ago, is sensitized, and will almost always respond to reinjection by exhibiting symptoms of serum sickness; only a small proportion fail in this respect.

Currie (1907) reported a case in which a rash appeared within 30 minutes of reinjection, spread over the whole body in 6 hours, and was gone in 24 hours. Goodall (1907) noted that an immediate reaction always occurred within 6 hours, and was sometimes severe but was not accompanied by joint pains. An accelerated reaction, on the other hand, was usually mild, consisting mainly of a rash, with or without fever, though sometimes joint pains also occurred. He further noted in some patients the occurrence of two or three distinct rashes separated by an interval of freedom, and ascribed these to the mixing of antiserum from different horses, each serum having a different sensitizing capacity.

There is no call here to discuss the underlying mechanism of sensitization. A great deal of work has been done upon it, and those who wish to study it are referred to the textbook by Humphrey and White (1964*a*).

Post-mortem examination of the few patients that have died from their primary illness during an attack of serum sickness has revealed the presence of lesions in the smaller vessels of numerous organs of the body indistinguishable from those met with in periarteritis nodosa, namely necrosis, fibrinoid alteration and hyalinization of the media, accompanied by perivascular infiltration with mononuclear and polymorphonuclear leucocytes (Rich 1942).

With the greatly diminished use of diphtheria antiserum in Europe and North America, the complete replacement of pneumococcal and meningococcal antiserum by chemotherapeutic agents, and the gradual adoption of active immunization against tetanus, together with the enzyme method of refining antiserum and the increasing use of human antiserum, serum sickness has become far less of a problem than it used to be.

13

ALLERGIC MANIFESTATIONS: SERUM NEURITIS

Serum neuritis

NEURITIS, usually of the Erb-Duchenne type affecting the 5th and 6th roots of the brachial plexus, is a well-recognized though uncommon sequel to the injection of horse serum. Most cases have been recorded after the prophylactic administration of tetanus antiserum. Whether this is because paralysis after therapeutic treatment with diphtheria antiserum has almost invariably been regarded as due to the effect of the diphtheritic toxin rather than of the antiserum; or whether it is because serum neuritis is mainly a disease of adults, who constitute the bulk of the patients receiving tetanus antiserum; or whether it is merely a statistical difference resulting from the far larger number of injections of tetanus than of diphtheria antiserum being given, it is difficult to say. There is probably some truth in all three explanations.

The recognition of the disease was slow. Engelmann (1897) in Germany is generally credited with having described the first case, but in view of the long incubation period—51 days—after the first injection of antiserum, the involvement of the leg rather than the arm, and the rapid recovery—one week—it may be doubted whether this was a genuine example of serum neuritis. Seven years later Grünberger (1904) described a somewhat similar case affecting the leg and passing off quickly, but with the much shorter incubation period of 13 days after the first injection.

The first typical case was recorded by Gangolphe (1908) in a man who contracted tetanus but was not given antiserum treatment till the 15th day of his illness. Eleven days later he complained of numbness of the left arm. Examination showed that the muscles of the forearm, and particularly of the fingers, were paralysed. There were sensory disturbances and the reflexes were abolished. The patient eventually made a good recovery.

Thaon (1912) was apparently the first to record a case after prophylactic tetanus antiserum. Neuritis did not develop for about a month. The right arm, including the scapular muscles and serratus magnus, was affected, and muscular atrophy set in. The further history of the patient is not given.

In the United States Richardson (1917) described a case of polyneuritis coming on three weeks after the cure of a patient who had received multiple doses of tetanus antiserum; and Dyke (1918) in England described a case of right brachial neuritis, accompanied by wasting, in a gunner coming on 15 days after the first of a series of three prophylactic injections of tetanus antiserum.

In France Lhermitte (1919) reported three cases of brachial paralysis with severe amyotrophy consequent on involvement of the 5th and 6th roots in the cervical region. There seemed little doubt that the tetanus antiserum was responsible. Sicard and Cantaloube (1923) reported three cases of paralysis affecting the muscles of the arm supplied by the radial nerve coming on about ten days after an injection of tetanus antiserum. They concluded that the nerve fibres had been constricted by inflammatory oedema in the groove in which they lay while winding round the humerus.

In 1924 Sicard, de Gennes and Coste, in describing four cases of paralysis of the upper extremities following the injection of diphtheria or of tetanus antiserum, suggested that paralysis was the result of compression by oedema of the nerve trunks as they emerged from the spinal column.

In the same year Blum and Pollet gave a general review of the various manifestations of serum disease; and Pollet gave an excellent review dealing specifically with the neurological manifestations. He found records in the literature of 25 cases of polyneuritis following the injection of serum, 18 of them after tetanus antiserum and 4 after diphtheria antiserum. No relation appeared to exist between either the site of the original trauma or the site of the injection and the group of nerves affected.

In 1925 Petit at Nancy devoted his doctoral thesis to 'Les Névrites Postsérotherapiques'. He analysed 39 cases dividing them into those suffering predominantly from motor disturbances (21), from sensory disturbances (5), or from mixed motor and sensory disturbances (13).

A. Motor group

In this group motor troubles appear usually about the 8th day causing clumsiness of certain movements. These are followed by paresis of the shoulder and arm, and then by flaccid paralysis and muscular atrophy. Not all the muscles of the arm are affected; sometimes paralysis is confined to the muscles supplied by a single nerve, for instance the radial. The motor troubles are preceded or accompanied by subjective sensory disturbances, such as numbness and formication, in the areas ultimately to be affected. The pains are spontaneous, fleeting, paroxysmal, piercing, sometimes atrocious, beginning at a particular spot and rapidly spreading to affect the whole limb in line with the main nerve trunks. Objective sensitivity remains intact. Usually only one limb is affected, but the disease may be bilateral, or occasionally affect all four limbs. The sensory disturbances seldom last more than a week, but may persist for a month. The motor troubles progress for a few days, weeks or months before gradually retrogressing. Muscles that have lost all electrical reactivity practically never recover.

B. Sensory-motor group

In this group, besides motor paralysis, both subjective and objective sensitivity are affected. Pains are often extensive and severe. Objectively, sensory disturbances, both superficial and deep, affecting touch heat and pain, are present. Ataxia of both upper and lower extremities is sometimes seen.

C. Sensory group

This group is characterized by subjective and objective sensory disturbances without any accompanying motor troubles. All four limbs may be affected or the sensory disturbances are localized and transitory.

Petit's classification follows that given by Pollet (1924), and is subject to a rigidity that is not always followed in practice. It is noteworthy, for example, that about thirty years later, Miller and Stanton (1954), though they distinguish between brachial radiculitis and polyneuritis, make no distinction between the motor and the sensory forms.

In 37 out of 39 of Petit's cases in which information was obtainable tetanus antiserum was responsible for 27, diphtheria antiserum for 3,

pneumococcal antiserum for 6, streptococcal antiserum for 2, and Marmorek's tuberculosis antiserum for 1. The doses used were 10–12 ml in twenty cases, 20–120 ml in eleven cases and up to 1340 ml in six cases. The frequency of dosage varied greatly; some patients had several injections in a single day, others two or three injections at 1-2-day intervals, and some daily injections for many days in succession. Nearly all injections were made subcutaneously. Thirty patients received serum for the first time, eight for the second, and one for the third. The age distribution ranged from 20 to 58 years. Twenty-nine of the patients were males and ten were females.

Petit could find no single aetiological factor to account for the predisposition towards neuritis; though he formed the opinion that the localization of the lesion was determined by the patient's professional occupation. Thus, practically all the males were affected in the arms, and the five soldiers in his series in the right arm. On the other hand, three women who were employed in lifting beds and whose crural nerves were compressed and stretched for months on end were affected in the legs.

Discussing pathogenesis, Petit dismisses Sicard and Cantaloube's (1923) explanation that the neuritis is due to compression of the nerve trunks by oedema in confined bony sites as purely hypothetical, and concludes himself that it is caused by the toxicity of the serum acting on a propitious subject—which is about as illuminating as that of the mode of action of morphine quoted by Molière in his satire on the medical profession.

Kennedy (1929) recorded five cases, three after tetanus antiserum and two after streptococcal antiserum; Bourrat (1929) one case after tetanus antiserum; and Bourguignon (1931) one case after diphtheria antiserum.

Allen (1931) reported one case coming on twelve days after an injection of antiscarlatinal serum, and reviewed 36 cases in the literature. He noted that the usual history was one of serum sickness developing 5-10 days after injection, characterized by general urticaria, fever, headache, vomiting, and pains in the limbs and joints. Two to five days later the pains became severe, intermittent and stabbing. They lasted for from two days to a month. Muscular weakness and wasting appeared early. Reflexes were diminished or abolished, and changes were observed in the electrical reactivity of the muscles. Improvement in motor function usually occurred when the pain subsided, but complete or almost complete recovery did not take place for 1-18 months. In 23 of Allen's cases neuritis was of the radicular type, the 5th and 6th cervical nerve roots being affected. In a further six cases only one nerve was affected. The remaining thirteen cases were of the polyneuritic type, characterized by general pains, clumsiness of the limbs, motor weakness, ataxic or steppage gait, and diminution of tendon reflexes and of sensation in the distal part of the limbs. In addition six cases were described of the cerebral type; these will be referred to under serum encephalitis (p. 206).

Young (1932) gave another review covering 40 cases, and added one case of his own. In addition he reported on seven cases of the cerebral type and three cases coming on after typhoid or staphylococcal vaccines (see Chapter 14). He noted that polyneuritis, though not uncommon, practically never resulted in paralysis of the lower limbs; it was the upper limbs that were the most susceptible. He doubted whether constriction of the nerve roots by oedema could explain all cases, because in some cases paralysis occurred in the absence of serum disease.

Wilson and Hadden (1932) described six cases, four after tetanus antiserum and two after diphtheria antiserum; and Bennett (1939) five

cases, four of the radicular brachial type and one of partial paralysis of the radial nerve. Bennett stated that about 115 authentic cases had been described in the literature during the previous thirty years. He said that, though most patients recovered in time, about 20 per cent were left with residual weakness and atrophy. He supported the view that the neuritis was due to perineural oedema leading to an ischaemic paralysis of the nerve trunks or peripheral nerves. Compression might occur in the intervertebral foramina, the bony grooves, or the perineural sheaths of the roots or of the nerves.

Elsässer (1942) in Bonn described five cases of polyneuritis coming on after injection of an antiserum; he referred to two more in a postscript. In one case half of the diaphragm was paralysed owing to involvement of the phrenic nerve; and, in another, tetraplegia of the Landry type was seen. Reviewing the literature, he found records of 30 cases in Germany between 1927 and 1942, and estimated that in the world as a whole about 200 cases must have been reported. In an analysis of 120 cases, including the German cases, he found paralysis of the upper-arm plexus in 58, paralysis of the muscles of the arm in 20 and of the leg in 2, extensive peripheral paralysis in 4, paralysis of the cranial nerves in 17, paralysis of the diaphragm in 3, disturbance of the central nervous system in 15, and in 1 case adrenal insufficiency. Three of the cases proved fatal, death occurring at the height of a paralytic illness of the Landry type. Broadly speaking, three-sixths of the cases were of paralysis of the shoulder girdle; in one-sixth there were other paralyses in addition to that of the shoulder girdle; in one-sixth there were circumscribed paralyses without upper-arm paralysis; and in the remaining one-sixth extensive paralysis, often of the Landry type, was present. The ultimate prognosis was good, though complete recovery in some cases took many years.

Kojis (1942), who contributed a long article on serum sickness, mentioned that only one case of serum neuritis was seen among 16 000 consecutive patients treated at the Willard Parker Hospital in New York, though how many of these had received serum injections is not stated. Hughes (1944) reported two cases after tetanus antiserum, and Mishkin (1949) one case in a man giving a negative skin test to antiserum. Garvey (1953) reported a series of 20 cases following the use of tetanus antiserum, in two of which there were associated cerebral symptoms. He made the point that the pain in serum neuritis is often so severe that the early paralytic features are masked.

Miller and Stanton (1954) contributed a useful review dealing with neurological complications after both vaccine and serum treatment. The frequency of neurological syndromes after serum treatment in 100 adequately documented cases was as follows:

(a) radiculitis, including brachial plexitis, 74 cases;

(b) polyneuritis and the Guillain-Barré syndrome (polyradiculoneuritis), 10 cases;

(c) Landry's paralysis and myelitis, 6 cases;

(d) cerebral and meningeal types, including optic neuritis, 10 cases.* They themselves described four cases of bilateral cervical radiculitis or polyradiculitis coming on after the administration of tetanus antiserum.

* For definition of the Guillain-Barré syndrome and of Landry's paralysis, see Leneman (1966).

Dickey (1955) described two cases of serum neuritis after tetanus antiserum. In one of these the deltoid, biceps and triceps muscles of the left arm were affected, though the serum had been injected into the right

arm. In the second case, in which symptoms of a more diffuse polyneuritis were added to those of brachial radiculitis, excruciating pains in the shoulders and at the back of the neck came on a week after the injection, and the arms, which became partly paralysed, remained painful. In both cases gradual improvement occurred over many months.

Bardenwerper (1962), reviewing the literature, stated that about 130 cases of neuritis had followed the use of tetanus antiserum prepared in horses. He added one case of his own. His article, like that of Miller and Stanton (1954), may well be consulted for further references to this subject. Finally, Freeman (1963) described one case of serum neuritis accompanied by muscular atrophy that came on after a simple test dose of 175 units of tetanus antiserum.

DISCUSSION

Serum neuritis has an incubation period of about 7 to 14 days. It is often, but not always, accompanied by symptoms of serum sickness—fever, headache, vomiting, urticaria, oedema, arthralgia. The intensity of the neuritis does not necessarily parallel that of the serum sickness. The origin of the serum, whether from horses, sheep or cattle, and the nature of the antitoxin, whether against diphtheria, tetanus, scarlatina, or other disease, appears to be immaterial. The neuritic paralysis, which begins with severe pains, is usually syammetrical, and affects the muscles of the shoulder girdle and upper arm (Germer 1965). The muscles of the lower limbs are seldom affected.

The incidence of post-serum neuritis is difficult to assess. Probably only a small proportion of the cases have been reported in the literature; and there seems to be no way of ascertaining the total number of injections of antiserum that have been given during the last 70 years. The fact, however, that several million doses of antiserum must be given every year throughout the world, and that the total number of recorded cases of serum neuritis probably does not exceed 200, indicates that this complication is comparatively rare occurring perhaps once in the course of 5-10 million injections, though this may well be an underestimate. What is noteworthy is that, whereas peripheral neuritis appears to be much commoner after sera than after vaccines, neurological sequelae affecting the central nervous system are commoner after vaccines than after sera.

Whether neuritis following cases of diphtheria or of tetanus is ascribable to the antiserum or to the bacillary toxin is not easy to say. In the first recorded case of neuritis after treatment with tetanus antiserum, Engelmann (1897) stated that the nervous symptoms did not appear till 51 days after the first injection. This is a very long incubation period for serum neuritis, as judged by that in patients given prophylactic serum only.

The possibility that neuritic lesions are caused by the bacillary toxin rather than by the antiserum is strengthened by the observation of Kollmann (1899) of a case of severe neuritis affecting the legs in a man who recovered from tetanus without the use of antiserum. A similar case is recorded by Hnátek (1905) in a woman treated without antiserum who suffered from brachial neuritis developing in the 4th week, just as she was getting better. Such an explanation, however, will hardly account for the far more numerous cases in patients that are given antiserum for prophylactic purposes and that never suffer from tetanus itself. It could be argued that in these cases a genuine infection with tetanus spores occurred and that toxin was formed in the tissues in an amount sufficient to cause

neural lesions but insufficient, as a result of the neutralizing action of the antitoxin, to cause manifest tetanus.

Most observers take the view that serum neuritis is a manifestation of allergy, mainly because it is seldom seen in the absence of serum sickness, and because the usual incubation period of 4-12 days corresponds to that of the normal immunological response of allergic patients. If this view is correct, it seems probable that the mechanism of production of the neuritis is one of constriction by oedema of the nerve roots as they emerge from the vertebral column as suggested by Sicard and Cantaloube (1923), or by oedema occurring in between the bundles of fibres in the main nerve trunks as suggested by Sézary and Dessaint (1923), that is, interfascicular as opposed to perineural oedema. The finding by Roger, Poursines and Recordier (1934) of oedema, small haemorrhages and interstitial neuritis of the brain, cord and nerve roots; and by Scheinker (1947), in a study often fatal cases of infectious poly-neuritis, of strangulation of the nerves at their points of exit from the dura mater lend support to this general conception.

An alternative explanation is that serum neuritis is merely an example of the acute brachial radiculitis, or 'shoulder-girdle syndrome' as Spillane (1943) calls it, that occurs in minor epidemic form or occasionally after such apparently precipitating factors as surgical operations, infections, accidents, or exposure to cold and rain. Wyburn-Mason (1941) at the Queen's Square Hospital in London saw 42 cases of brachial neuritis in eight months, and mentioned that Dr J. Purdon Martin had seen a similar series of cases. Spillane (1943) analysed 46 cases, and concluded that the essential lesion was one affecting the peripheral nerves rather than the brachial plexus or nerve roots. Turner (1944) described 36 cases coming on 2-10 days after what he regarded as a precipitating factor; and Parsonage and Turner (1948), who observed 136 cases in the Army between 1941 and 1945, argued that the clinical similarity of these cases to those of serum neuritis was so close that they must be regarded as having the same aetiology.

Whatever the explanation, there is no doubt that brachial neuritis must be included among the more serious hazards of serum administration. Not only is the disease extremely painful and characterized often by a long period of muscular disability, but in something like 20 per cent of cases it leaves behind it permanent weakness or paralysis.

14

ALLERGIC MANIFESTATIONS: POST-VACGINAL NEURITIS

Post-vaccinal neuritis

AS HAS already been pointed out, neuritis is far less common after vaccine than after serum treatment, possibly because of the much smaller amount of antigenic material injected. Most neurological complications after vaccines are of the myelitic or encephalitic type (see p. 157).

Jumentié (1916) was apparently the first to describe a case of post-vaccinal neuritis. A soldier aged 34 years was given two injections of typhoid vaccine in January 1915 and another two 3 months later. On the same day as that on which he received this second injection he suffered from pain in the shoulder. During the next few days the pain spread to the knees and other joints of the lower limbs. A year later he was still in hospital diagnosed as a case of polyneuritis. There was no paralysis, but deep sensitivity was disturbed, the gait was ataxic, and movements were slow and uncertain. Loss of equilibrium was noticeable on both standing and sitting. Pains were intermittent, partly muscular, partly periarticular, made worse by walking, irresponsive to treatment, and as bad as they were when the illness began. In addition the sympathetic system was affected. There was profuse sweating of the right half of the face and of the left hand, right exophthalmos, and paralysis of the internal rectus muscle of the left eye.

Three years later Preti (1919) in Italy reported two cases. In the first a soldier was given a single dose of typhoid vaccine. A severe local and constitutional reaction followed with fever lasting for over a week. On the 3rd night the patient woke up to find himself blind. Blindness persisted for ten days, after which the temperature fell and the patient partly regained his vision. When seen six months later, he was still partly blind. The ophthalmological diagnosis was optic neuritis followed by partial atrophy. In Preti's second case a soldier was given two doses of a typhoid-paratyphoid vaccine at 10 days' interval. After the second injection he had a violent constitutional reaction lasting four days. A fortnight later recurrent convulsions of the left arm and face began. On one occasion they became generalized, and were accompanied by trismus, the secretion of bloody saliva, abolition of the cranial reflexes and loss of consciousness. When seen a year later, the left arm was weak and subject to frequent convulsions, which were ascribed to an area of irritation in the right inferior rolandic zone. Neither of these cases was one of peripheral neuritis, but they are recorded here because of their historical interest.

Kennedy (1929) in the United States reported one case of polyneuritis in a man of 34. The day after his second injection of typhoid vaccine, the patient had a severe reaction consisting of high fever and urticaria. Numbness of the feet came on, spread slowly up to the waist and later affected the fingers. There was trouble in focusing near objects, an incomplete glove-and-stocking anaesthesia, a weak and awkward grasp, and desperate tiredness. These symptoms lasted for eight weeks before gradually retrogressing.

Allen (1931) met with one case of neuritis after typhoid vaccine, and Young (1932) two cases after typhoid vaccine and one case after

staphylococcal vaccine. Robinson (1937) described a case of unilateral flaccid peripheral paralysis coming on four days after the second dose of TAB vaccine. Both injections were made into the deltoid muscle—the second being on the right side—but paralysis affected the muscles of the left leg and resulted in foot drop. No improvement was noted under physiotherapy for three months, after which rapid and complete cure occurred spontaneously. In this case there were no fever, no muscular pain, and no change in the cerebrospinal fluid.

Hughes (1944) reported four cases, one after tetanus toxoid and three after TAB vaccine. The one following tetanus toxoid began ten days after the last of a series of injections and was characterized by slurring of the speech, nystagmoid movements of the eyes, and left hemiparesis. The patient had only partly recovered when seen four months later. One patient given intravenous TAB for the treatment of gonorrhoea suffered ten days later from right musculospiral palsy; he recovered within three months. Two patients given TAB prophylactically suffered 10 and 14 days later from brachial palsy of the radicular type, causing weakness of the shoulder muscles. One recovered completely, but not the other, who showed muscular wasting. It is probable, but not expressly stated, that all three of the patients given TAB vaccine had been previously immunized with this vaccine prophylactically. Peacher and Robertson (1945) likewise met with a case of right-sided brachial palsy accompanied by pain and paraesthesia coming on in a soldier one week after a reinforcing dose of TAB vaccine; examination revealed atrophy of the shoulder muscles.

Miller and Stanton (1954), whose review on the neurological sequelae of prophylactic inoculation should be consulted, collected records of twelve cases of radiculitis, plexitis, or mono-neuritis after TAB vaccine and eight cases of polyneuritis and the Guillain-Barré syndrome. They refer to a still larger number of cases in which the central nervous system was affected (see p. 194). They express the opinion that anaphylactic sensitivity underlies all these neurological complications.

One case of brachial neuritis coming on the day after a third injection with Salk's poliomyelitis vaccine is described by Berglund (1963) in a woman 45 years of age. The arm affected was the one into which the injection had been made. Berglund notes that there was a severe local reaction at the injection site. No pathogenic agent could be detected either in the faeces or in the cerebrospinal fluid.

A few cases of paralysis caused apparently by neuritis have been recorded after immunization against diphtheria; they have been collected and tabulated by van Ramshorst and Ehrengut (1965). It is not improbable that their number has been underestimated, and that many cases have been regarded as purely coincidental. Clinically they have mostly taken the form of ocular, palatal, facial and crural paralyses, as in the natural complications of the disease itself.

DISCUSSION

It would be more correct to refer to the cases just described as neurological complications of vaccine treatment than as post-vaccinal neuritis. In some of them the cranial nerves and the brain were affected. Only a few suffered from neuritis of the peripheral nerves. Such a small number of these cases have been reported that it is difficult to generalize on them. As in serum neuritis, there is usually a lapse of 7-10 days after the injection before nervous symptoms appear. There is, of course, no serum disease, but a severe constitutional reaction seems to be fairly common. Cases are apparently more frequent after a second than after a first injection.

Children, as in serum neuritis, are spared. The aetiology of these cases is obscure, but it seems reasonable to suppose that allergy plays a part.

15

ALLERGIC MANIFESTATIONS: ENCEPHALOMYELITIS AFTER SMALLPOX VACCINE

Post-vaccinal encephalomyelitis

History. The literature on this subject is extensive, and there seems no justification here for giving more than a general outline of the findings. The early work is summarized in the report (1925) of the Andrewes Committee, and in the two reports (1928*b*, 1930) of the Rolleston Committee on Vaccination appointed by the Ministry of Health in 1926. More recent reviews have been made by Thompson (1931), Stuart (1947), Conybeare (1948, 1964), Winkle and Salchow (1956), de Vries (1960), Weber and Lange (1961), Herrlich, Ehrengut and Schleussing (1965*a*) and Buchwald (1965).

At what date nervous complications of vaccination first occurred is doubtful. According to Kaiser and Zappert (1938), post-vaccinal encephalomyelitis is not a new phenomenon. In Bohemia in 1801 and 1802 there were 35 cases of disease affecting the central nervous system among 10 090 persons vaccinated against smallpox; and cases had been described as early as 1768 by a Viennese doctor, Doctor Rechberger, after variolation. Little was heard of the disease during the first six or seven decades of the nineteenth century. This is ascribed by Lentz and Gins (1927) and Winkle and Salchow (1956) to the decline in virulence of the vaccinia virus as a result of repeated arm-to-arm passage, and to the addition of glycerol that was recommended in 1866 by Müller to protect the vaccine against bacterial and mould contamination. (It may be noted that, according to Collier (1954), Cheyne, an English physician, was the first, in 1850, to advocate the use of glycerol for this purpose.) The glycerolated lymph was kept at room temperature and lost much of its virulence. Restoration of virulence was assured by alternate rabbit and calf passages that were adopted indirectly as the result of the work of Calmette and Guérin (1901) on rabbits. Now that lymph through alternate passage and early harvesting is highly virulent, Winkle and Salchow maintain that post-vaccinal encephalitis is commoner than before.

Comby (1907) in France appears to have been the first to record the history of an individual case seen in 1905, though, according to Winkelman and Gotten (1935), Westphal in Germany is said to have reported a fatal case of post-vaccinal disseminated myelitis in 1874 and described the findings at autopsy. (I have not been able to confirm this statement. Westphal (1874, 1876) described seven cases of myelitis, two of which came on after smallpox, but I can find no mention of any case after vaccination.)

Comby's report was followed in 1912 by a case at the London Hospital studied by Turnbull (see Turnbull and Mclntosh 1926), and one in the same year in Frankfurt-am-Main (Report 1959*a*). In 1926 Turnbull and Mclntosh described seven cases—one observed in 1912 and six observed in 1922 and 1923—-and gave a clear account of the clinical picture and the histological changes. Meanwhile Lucksch (1924) in Prague had described three fatal cases seen in 1923; and Bastiaanse (1925) in the Netherlands had collected a total of 34 cases seen during 1924 and the

early part of 1925. In England Winnicott and Gibbs (1926) reported one case of their own, and gave brief accounts of 43 other cases appearing in the world literature. The Andrewes Committee (Report 1925) investigated 63 cases in England and Wales, the Rolleston Committee (Report 1928*b*) 30 cases, and the Rolleston Committee (Report 1930) a further 90 cases. In 1927 the disease was made notifiable in Austria, and by 1935 a total of 270 cases, of which 240 were regarded as genuine, had been reported there (Kaiser and Zappert 1938).

Though Lucksch (1924) at first regarded the disease as related to encephalitis lethargica, which was prevalent in the twenties, and Mclntosh (see Report 1928*b*, Mclntosh and Scarff 1930) as caused by a vaccinial infection of the central nervous system, it was soon realized that histologically the characteristic lesions were indistinguishable from those seen in cases of encephalitis following variola, varicella, measles, and influenza (Perdrau 1928, Greenfield 1930, Lucksch 1932). Repeated failure to demonstrate the vaccinia virus in the brain of typical cases led to the conclusion that encephalitis following vaccinia and certain other viral infections was due either to the activation of an unknown virus or to allergic sensitization (Report 1928*b*). Work of more recent years has tended to favour the second alternative.

Histological appearances. The characteristic lesions in post-vaccinal encephalitis were first clearly described by Turnbull and Mclntosh (1926). They drew attention (a) to the number and size of the zones of extra-adventitial perivascular infiltration in contrast to the normal sharply defined vascular sleeves, often limited to a single row of cells, within the adventitia; and (b) to the broad perivascular zones of softening in the white matter where cellular infiltration was comparatively slight. They noted the extensive involvement of the grey and white matter of both cerebral cortex and spinal cord, particularly the pons and the lumbar and upper sacral cord; and they pointed out that these lesions differed from those seen in poliomyelitis and, though to a less extent, from those in encephalitis lethargica.

Perdrau (1928) confirmed these findings and agreed in concluding that the characteristic lesion of post-vaccinal encephalitis was perivascular demyelination, which he regarded as corresponding to Turnbull and Mclntosh's areas of softening.

In amplification, it may be said that meningeal inflammation is slight and irregular; that the nerve cells themselves are little affected; that advanced neuronophagia is absent; that the perivascular demyelination of the medullary sheaths is accompanied by destruction of the axis cylinders; that the perivascular spaces contain many lymphocytes and the demyelinated areas lymphocytes and highly pleomorphic microglia; and that similar lesions are met with in the post-infection encephalitides (see Perdrau 1928, Greenfield 1930, Sjövall 1932, Hurst 1953).

More recently, de Vries (1960) put forward the view that post-vaccinal encephalitis comprises several pathologically different diseases of the central nervous system. He divides the cases into two broad groups—those occurring in persons over two years of age and those occurring in infants under this age. The first group, corresponding to the demyelinating form described by Turnbull and Mclntosh (1926), he calls 'peri-venous' or 'microglial encephalitis', and says that it is commoner after vaccinia than after any of the natural infectious diseases of childhood. Its main characters are perivenous demyelination and microglial proliferation in the demyelinated area, with or without slight changes in the vessel wall.

There is slight diffuse infiltration of the pia mater with lymphocytes; marginal gliosis; an absence of polymorphonuclear or red cells; and no more than slight and inconspicuous oedema.

On the other hand, in the second group, the changes seen in the brain of infants under two years of age are essentially vascular, including general hyperaemia of the brain; oedema either general or perivascular; mild lymphocytic infiltration of the meninges and some perivascular spaces; widespread degenerative changes of ganglion cells; and sometimes perivascular haemorrhages. Disease characterized by these changes he would refer to as 'encephalopathy'. de Vries regards the aetiology of these two main forms as distinct (see p. 174). So also do Keuter (i960) and Weber and Lange (1961).

Other forms of encephalitis, such as the subacute leucoencephalitis of van Bogaert, have been described after smallpox vaccination, but the paucity of cases prevents any firm conclusion on cause and effect (see Caruso, Minicuci and Conti 1964).

Clinical features. In the perivenous demyelinating microglial encephalitis following vaccination in persons over two years of age the onset is usually abrupt with fever, vomiting, headache, malaise, and anorexia, succeeded by such symptoms as loss of consciousness, amnesia, confusion, disorientation, restlessness and delirium, drowsiness, convulsions and coma, with incontinence or retention of urine, obstinate constipation, and sometimes meningismus. Paralysis, when it occurs, tends to be of the upper neurone type. The spinal fluid shows a lymphocytic reaction and an increase in protein. The case-fatality rate fluctuates around 35 per cent. In fatal cases death usually occurs within a week. In patients that survive, recovery often sets in within a few days and is complete within a fortnight. Permanent sequelae are unusual (Bastiaanse 1925, Kaiser and Zappert 1938, Greenberg 1948, Report 1944). Weber and Lange (1961) regard somnolence, unconsciousness, convulsions, paralyses and meningeal symptoms as alone indicative of cerebral disturbance. Fever, headache, vomiting and restlessness are not significant, because they cannot be distinguished from the normal vaccinal reaction.

The disease varies in its manifestations (see Report 1944, Conybeare 1948, Report 1959*a*, Spillane and Wells 1964). It may take the form of an acute myelitis (Troup and Hurst 1930, Kaiser and Zappert 1938, Conybeare 1948, Spillane and Wells 1964), but commonly the spinal symptoms are overshadowed by those of encephalitis (Conybeare 1948). Sometimes meningeal symptoms—headache, stiffness of the neck, head retraction—predominate, though Spillane and Wells (1964) would regard these cases as representing the meningism of viraemia rather than true encephalitis. Cases of true meningo-encephalitis may, however, occur (Vondarev 1964, Spillane and Wells 1964). Epilepsy may also be initiated or provoked by vaccination (Spillane and Wells 1964, Vondarev 1964).

The differential diagnosis of post-vaccinal encephalomyelitis is not always easy to make from poliomyelitis coming on after vaccination. An acute onset and the occurrence of frequent convulsions and of spastic lesions or other pyramidal symptoms are in favour of encephalitis (Min-Sen Li 1940, Report 1959*a*); but the diagnosis can be established with certainty only by virological examination in the laboratory, a search being made for poliovirus in the stools and for a rise in neutralizing antibodies (Linneweh and Oehme 1957).

There is no doubt that the disease is often diagnosed wrongly. Gins (1933) quoted 16 cases regarded during life as post-vaccinal encephalitis

that were found at autopsy to be due to other causes; and numerous workers have recorded cases that failed to show on histological examination of the central nervous system the typical lesions of perivenous demyelinating microglial encephalitis. Some of these cases, occurring in infants, may well have been what de Vries (1960) refers to as encephalopathy. For a discussion on differential diagnosis reference should be made to the article by Herrlich, Ehrengut and Schleussing (1965*a*).

The clinical manifestations of the *encephalopathy* seen in infants under two years of age are varied. The disease is often fulminant and over half the cases may prove fatal on the first day of cerebral manifestations. At post-mortem a miscellany of lesions may be found, such as those of poliomyelitis, meningococcal meningitis, embolism, sinus thrombosis, oedema, pneumonia, enteritis or toxaemia (de Vries 1960). According to Spillane and Wells (1964) the onset in cases of encephalopathy is often explosive with convulsions; hemiplegia and aphasia are common; the period of amnesia is short; the spinal fluid, though under increased pressure, is often normal; and recovery is frequently incomplete, the patient being left with cerebral impairment and hemiplegia. One patient—a baby girl aged 3 months—diagnosed as post-vaccinal encephalitis during life, was found, on subsequent post-mortem and virological examination, to have died from an acute viraemia. Up till the morning of the ninth day the vaccinal reaction appeared to be taking its normal course; then within a few hours the infant died quite suddenly in a state of hyperthermia. Vaccinia virus was isolated from the spleen, heart and bone marrow, though not from the brain. The cerebral vessels were congested but the brain showed no evidence of inflammation (Apostolov, Flewett and Thompson 1961).

The length of the *incubation period* in post-vaccinal encephalitic disturbances is open to question. A range of 2 to 34 days has been suggested, but there is reason to doubt the genuineness of cases at the extreme limits. Kaiser and Zappert (1938) put it at 5-15 days with only a very occasional case falling outside this range. Their contention is strongly borne out by the study of Weber and Lange (1961). These workers analysed the incubation period in 265 cases of post-vaccinal cerebral disturbance which both clinically and pathologically could be regarded as causally related to vaccination. They divided them into three groups (Table 3).

TABLE 3. Length of the incubation period in 265 cases of post-vaccinal cerebral damage (Weber and Lange 1961)

Incubation period in days	Group I Primary vaccination Encephalopathy		Group II Primary vaccination Post-vaccinal encephalomyelitis		Group III Revaccination Post-vaccinal encephalitis
	No. of cases	%	No. of cases	%	No. of cases
4	2	2·04	0	—	0
5	3	3·06	2	1·24	0
6	12	12·24	0	—	2
7	13	13·27	1	0·62	1
8	17	17·35	6	3·73	0
9	24	24·49	8	4·97	0
10	10	10·20	6	3·73	1
11	5	5·10	21	13·04	1
12	3	3·06	37	22·98	0
13	3	3·06	31	19·25	1
14	4	4·08	31	19·25	0
15	1	1·02	12	7·45	0
16	0	—	3	1·86	0
17	0	—	1	0·62	0
18	1	1·02	2	1·24	0
Age up to 2 years	96	98	7	4·3	6
Age over 2 years	2	2	154	95·7	—
Total	98		161		

It will be seen that 98 per cent of cases up to two years of age presented the picture of an encephalopathy, whereas in those over two years 95.7 per cent presented that of a true encephalomyelitis. In the under-two-year group the median incubation period was 8.64 ± 2.26 days, in the over-two-year group it was 12.33 ± 2.12 days. In other words the cases suffering from encephalopathy had an incubation period nearly four days shorter than those suffering from encephalomyelitis.

The two groups also differed in the rate of evolution of their illness. The average time to death after vaccination was 10.48 ± 2.95 days in group I and 16.26 ± 3.89 days in group II, showing that the duration of the disease after the onset of cerebral symptoms was shorter in cases of encephalopathy than in those of encephalomyelitis. But in both groups the range of the incubation period was 4 to 18 days. The six cases occurring after revaccination also had an incubation period within this range, though pathologically they presented a picture differing in some respects from that of true encephalomyelitis cases.

The cranial nerves may be involved in the encephalitic process, but occasionally they are affected in the absence of any other lesion of the brain or cord. Agarwal, Dayal and Agarwal (1963), for example, described a case of bilateral neuroretinitis in a woman coming on three days after revaccination and clearing up under corticosteroid therapy. No other abnormality could be detected.

Besides lesions of the central nervous system, the peripheral nerves may be affected. In their study of 39 cases of a neurological disorder following vaccination, Spillane and Wells (1964) had five patients suffering from polyneuritis and two from brachial neuritis.

EPIDEMIOLOGY

Incidence. The incidence of post-vaccinal encephalomyelitis has varied greatly in different countries. Such figures as are available are summarized in Table 4, which classifies the cases according to whether they followed primary vaccination or all vaccinations, i.e. both primary and revaccination.

TABLE 4. Incidence of post-vaccinal encephalitis in different countries after primary vaccination and after all vaccinations (primary and revaccination)

Country		Cases/ Vaccinations	Rate per million	Country		Cases/ Vaccinations	Rate per million
Netherlands	1924–27 a	168/657 000	256	England and Wales	1922–27 j	93/4 540 000	20
Netherlands	1930–43 b	79/602 079	130	England and Wales	1928–29 j	90/4 350 000	21
Netherlands	1947 c	72/86 800	829	England and Wales	1930–46 k	115/5 100 000	23
Italy	1936–37 d	11/1 104 000	10	England and Wales	1951–60 l	64/5 060 000	13
Austria	1948–53 e	32/79 761	401	Scotland	1942 m	46/935 300	49
Hamburg	1939–58 f	46/390 104	118	German Federal Republic	1926–36 n	168/23 370 000	7
German Federal Republic	1950–57 f	455/6 106 600	75	Netherlands	1929 g	82/1 500 000	55
Bavaria	1945–53 h_1	75/1 150 000	65	Sweden	1924–28 c	20/422 827	47
Bavaria	1953–62 h	182/1 446 832	126	Belgium	1948 c	26/18 000	1444
Switzerland	1940–46 g	43/800 000	54	New York	1947 c	45/5 000 000	9
USA	1963 i	11/6 200 000	18	Austria	1925–37 c	282/1 128 000	250
				Norway	1933–37 n	28/112 300	249
Total		1173/18 623 097	63	*Total*		1059/51 536 427	21

a. Jitta (1930). b. van den Berg (1946). c. Herrlich (1952). d. Müller (1946). e. Berger and Puntigam (1954).
f. Seelemann (1960). g. Stuart (1947). h_1 Herrlich (1954). h. Herrlich, Ehrengut and Schleussing (1965*d*). i. Neff (1965).
j. Estimates from Jubb (1943), Reports (1925, 1928*b*, 1930). k. Estimate from figures given by Conybeare (1948).
l. Conybeare (1964). m. Anderson and McKenzie (1942), Fyfe and Fleming (1943), Report (1944). n. Herrlich (1952).

It is to be noted that the denominators given for the years 1922 to 1946 for England and Wales are merely estimates and not like those for 1951 to 1960 which were derived from records of vaccinations done under the National Health Service and returned annually to the Ministry of Health by the Local Health Authorities.

In addition, the following figures may be quoted from Stuart (1947) and Herrlich (1952); they refer to all vaccinations.

	Incidence
Belgium 1932-6	1 in 150,000 or 7 per million vaccinations
Finland 1937	1 in 32,400 or 31 per million vaccinations

In France and Greece the disease appears to have been very uncommon. Figures for small groups, figures in which it is not clear whether they refer to primary vaccination or to all vaccinations, and Terburgh's figures (1927), which refer to the first two years of life only, have been omitted.

Judged by the rate per million vaccinations the incidence of post-vaccinal encephalitis has been highest in the Netherlands, Austria and Germany. The very high figure, namely 1444 per million, for Belgium in 1948 is exceptional, but does tally to some extent with the high incidence in the neighbouring countries of Holland and Germany.

In the Scottish outbreak of smallpox in 1942 the incidence of post-vaccinal encephalitis, 49 per million, was more than double that in England and Wales during the same period. This can probably be explained by the fact that a high proportion of persons vaccinated in Scotland were older children and adults, in whom, as will be seen later, the disease is commoner than in younger children.

It will be noted that the incidence was over four times as high after primary vaccinations as after all vaccinations. Without knowing the number of primary vaccinations and of revaccinations, this figure does not mean very much.

Local aggregation. The figures that have just been given show the wide variation in incidence of post-vaccinal encephalomyelitis between different countries. Apart from this, however, numerous workers have noted within a given country a great variation in incidence, and the frequent aggregation of cases in both place and time. For example, Bastiaanse (1925) in Holland remarked on the tendency of cases to occur in groups, and for two or three subjects to be affected simultaneously.

Villages were affected more than small towns. Again in Holland, it was noted that the incidence ranged from 19 per million primary vaccinations in Limbourg to 526 per million in Groningen (Jitta 1930), and on the Island of Marken to 83 000 per million (Thompson 1931). In Austria, according to Kaiser and Zappert (1938), most of the cases were concentrated in the Tyrol where the incidence was 425 per million vaccinations. In Burgenland, on the other hand, which was the only province in Austria in which vaccination was compulsory, the incidence was only 14 per million. In Bavaria analysis of the figures revealed a grouping of cases along the waterways, such as the valleys of the Inn, Main and Danube (Herrlich, Ehrengut and Weber 1956). In Germany during 1948-50 the incidence ranged from 7 per 1 000 000 primary vaccinations in Bavaria to 226 in Hessen (Report 1959*a*). In Müller's (1946) small series of 15 cases in Basle, 2 were in sisters.

Most striking were the observations in England and Wales recorded by the Andrewes Committee (1925). In 1923 three cases occurred within 3 days of each other in a small town, Bedwellty, in Monmouthshire, and four cases in another small town, Tredegar, in the same county. All the cases were in school children. In face of such a distribution it is difficult to escape the conclusion that some factor concerned either with the vaccine itself, with the prevalent viral flora in the community at the time, or with some peculiar local susceptibility of the population must have been in operation.

Relation to age. Though the figures of observers in different countries are not in complete agreement with each other, they all point to an increasing liability to post-vaccinal encephalomyelitis with advancing age—at least up to 12 years. The main discrepancies occur over the incidence in the first two years of life; is it commoner in the first year or the second? In view of the evidence brought by de Vries (1960) and Weber and Lange (1961) that infants under two years do not suffer from a true demyelinating encephalomyelitis, discussion of this question seems pointless. What is clear is that the disease has its highest incidence between 6 and 12 years of age. Instead of going in detail through the records, it will be simpler to give a table summarizing the results of the major series of cases as recorded by different observers (Table 5).

TABLE 5. Primary vaccination. Incidence of post-vaccinal encephalomyelitis in relation to age
Number of cases/number of vaccinations. In parenthesis, rate per million vaccinations

Age in years	van den Berg (1946) Holland 1924–8	Stuart (1947) Holland 1930–43	Müller (1946) Basle 1944–5	Stuart (1947) Femmer (1948) Düsseldorf 1948	Herrlich (1954) Bavaria 1945–53	Berger and Puntigam (1954) Austria 1948–53	Seelemann (1960) Hamburg 1939–58	Conybeare (1964) England and Wales 1951–60	Total
0–	6/155 730 (39)	22/441 294 (50)	0/826	0/28 768	56/1 008 000 (56)	6/58 438 (103)	34/367 390 (93)	40/2 960 406 (14)	130/4 663 595 (28)
2–	43/281 694 (153)	11/78 417 (140)	0/1269	2/29 370 (68)	11/117 000 (94)	3/14 860 (202)		2/188 134 (11)	108/1 115 492 (97)
4–	69/222 920 (310)	12/43 653 (275)	3/1139 (2634)	5/32 367 (154)	3/14 000 (214)	6/4138 (1450)	6/11 461‡ (524)	8/264 316‖ (30)	111/782 185 (142)
6–	15/43 806 (342)	31/29 382 (1055)	3/1579† (1900)	7/5 331 (1313)	3/9800 (306)	10/1598 (6258)	—	—	69/91 496 (754)
12 and over	—	2/9323* (215)	—	—	—	7/727 (9629)	6/15 252§ (393)	16/407 513¶ (15)	22/1 437 050 (15)

* 11 and over (van den Berg 1946). † 6–10. ‡ 4–9 years. § Over 9 years. ‖ 5–14 years. ¶ Over 15 years.

The figures for over 12 years are too few to serve for satisfactory comparison and are grossly overweighted by the English experience, but, such as they are, with the exception of Berger and Puntigam's (1954) small series, they show a decline after this age. According to Conybeare (1948) figures in the Netherlands indicate that the disease is 10-30 times as common after primary vaccination at school age as in infancy.

Relation to revaccination. There is a general consensus of opinion that encephalitis is much less common after revaccination than after primary vaccination. All the available figures support this, but the figures themselves are, in general, so unsatisfactory that the magnitude of the difference cannot be measured.

Apart from the fact that some of the figures are little better than guesses, it is difficult to know exactly what is meant by revaccination. Many so-called revaccinations are in reality primary vaccinations, either because some other type of vaccination, such as with BCG, performed at an earlier date has been confused by the patient with smallpox vaccination, or because the primary vaccination never took and the patient remained unimmunized (Kaiser and Zappert 1938, Seelemann 1960), de Vries (1960) goes so far as to question whether encephalitis ever follows genuine revaccination. He quotes Bastiaanse as saying that the typical microglial type of encephalitis was never seen at autopsy in a case in which revaccination had resulted in an immune reaction, de Vries himself states that, in his own experience, microglial encephalitis never occurs after revaccination when partial immunity is present. He maintains too that the type of encephalitis that follows revaccination has a wider range of incubation period, a greater degree of clinical variation, and a higher proportion of neurological sequelae in those that recover than has the true microglial form.

Nanning (1962) gives the incidence of encephalitis in the Netherlands as 250 per million after primary vaccination and 20 per million after revaccination. For England and Wales during 1951-60 the incidence at all ages after primary vaccination is given as 15 per million and after revaccination as 8 per million (Conybeare 1964). It may be noted, however, that in the English series not a single case occurred after revaccination of 235 682 children under 15 years of age; the eight cases that did occur among 1 004 962 revaccinated persons were all over this age. The figures for Italy during 1936-7 reveal an incidence of 11/1 104 000 cases or 10 per million for primary vaccination, and of 0/1 205 000 or less than 1 per million for revaccination.

Effect of other factors. No constant relation has been found between the type of vaccine used or the method of vaccination and the occurrence of encephalitis.

On the other hand Keuter (1960) brings evidence to show that the disease occurs mainly in persons with some constitutional abnormality or belonging to abnormal families. The commonest disturbances are neurological, psychiatric, epileptic, allergic and endocrine. It is probable that many of the encephalopathies, marked by convulsions, meningismus, paralyses, sinus thrombosis, cerebral oedema, or toxaemia, which occur in infants under two years of age and are reported as post-vaccinal encephalitis, are in fact manifestations of an unstable inheritance and would have occurred after some other stimulus had vaccination not been performed. It was apparently for this reason that the Ministry of Health recommended the postponement of vaccination till the second year of life,

by which time a number of these infants would already have succumbed to intercurrent illness (Report 1963). Keuter's contention is in agreement with Herrlich's (1954) finding that, of 75 cases in Bavaria during the years 1945-53, no fewer than 55 were in infants and children suffering from a congenital nervous defect or from some actual disease. In Müller's (1946) series of 15 cases in Basle, three occurred in children vaccinated shortly after an infective disease—pertussis, mumps and tetanus. Further evidence pointing in the same direction is reviewed in the report of the German Health Office (1959*a*).

Case-fatality rate. Table 6 summarizes the main reports on the fatality rate of cases of post-vaccinal encephalitis.

TABLE 6. Case-fatality rate of post-vaccinal encephalitis

Country		Deaths/ cases	CFR %	Country		Deaths/ cases	CFR %
Netherlands	1924–27 a	52/168	31	Scotland	1942 j	14/46	30
Netherlands	1930–43 b	24/78	31	England and Wales	1922–24 k	36/63	57
Austria	1925–37 b	77/282	27	England and Wales	1924–27 l	16/30	53
Hamburg	1939–58 c	14/46	30	England and Wales	1928–29 m	42/90	47
Bavaria	1945–53 d	40/75	53	England and Wales	1930–46 n	58/115	50
Basle	1944–45 e	2/15	13	England and Wales	1951–60 n	22/64	34
Germany	1930–36 f	37/111	33	USA probably	1955–60 o	3/12	25
Germany (Bundesgebiet)	1945–51 f	106/263	40	USA	1960–63 p	1/5	20
Switzerland	1940–46 g	12/43	28	USA	1963 q	4/11	36
German Federal Republic	1950–57 c	150/455	33				
German Federal Republic	1953–62 h	112/381	29				
New York	1947 i	4/45	9	*Total*		826/2398	34

a. Jitta (1930). b. Herrlich (1952). c. Seelemann (1960). d. Herrlich *et al.* (1954). e. Müller (1946).
f. Winkle and Salchow (1956). g. Stuart (1947). h. Herrlich (1964). i. Greenberg (1948).
j. For references see Table 4, p. 165. k. Report (1925). l. Report (1928*b*). m. Report (1930).
n. Conybeare (1964). o. Kempe (1960). p. Sussman and Grossman (1965). q. Neff (1965).

Except for the low rate of 9 per cent for New York in 1947, where most of the vaccinations were in adults, and of 13 per cent for Basle in 1944-5, and the high rates of 57 and 53 per cent for England and Wales during the years 1922-7, the range in case-fatality rates for the different countries is not great. The arithmetic mean for all cases listed in the table is 34 per cent.

Little information is available on the relation of mortality to age. Seelemann (1960) says that in Hamburg from 1939 to 1958 the case-fatality rate was 38 per cent in children under four years and only 8 per cent in those over this age. The greater risk of death in infants and young children is borne out by the figures for England and Wales from 1922 to 1960, where the fatality rate is seen to have decreased from 62 per cent in infants to 40 per cent in adolescents and adults (Table 7).

TABLE 7. Relation of case-fatality rate to age in post-vaccinal encephalitis for England and Wales 1922-60 (Conybeare 1964)

Age in years	Deaths/cases	Percentage case-fatality rate
< 2	48/78	62
2-4	4/6	67
5-14	75/158	47
15 and over	47/118	40

AETIOLOGY

This is not the place to enter into a detailed discussion of the pathogenesis of post-vaccinal encephalomyelitis. Briefly, there are three main views.

(a) That it is caused by the vaccinia virus itself. This view was favoured by Mclntosh and Scarff (1930), Eckstein (1931) and Griffith (1952) among others and apparently also by Környey (1943) who, in an extensive review, regarded the demyelinating encephalitides as being probably due to a generalized virus infection. Its weakness lies partly in the failure to demonstrate vaccinia virus in the central nervous system of cases of the disease, and partly in the failure to produce experimentally in animals a demyelinating encephalitis by the injection of vaccinia virus. It is not difficult to infect the brain with this virus, but the resulting inflammatory disease is dominated by meningitis, and the histological picture is quite different from that seen in human post-vaccinal encephalitis (Hurst 1953). In infants an overwhelming viraemia may be seen, in which vaccinia virus is abundant in the brain, but here again the histological picture is that of an encephalopathy and not of a demyelinating microglial encephalitis (Conybeare 1964).

(b) That it is caused by a latent neurotropic virus in the body which is activated by the vaccinia virus. This was the view put forward by Bastiaanse (1925), by the Andrewes Committee (Report 1925) and by the Rolleston Committee on Vaccination (Report 1928*b*) and was upheld by Ledingham (1934) and various other workers. Unfortunately no satisfactory evidence in its support has yet been forthcoming. Experimental attempts to reproduce post-vaccinal encephalitis with herpes or polio-virus have been unsuccessful (Berger 1929, Hurst and Fair-brother 1931), as have likewise attempts to demonstrate a neurotropic virus in the brain of human patients (Hurst 1953). More recently, however, Zu Rhein and Shi-Ming Chou (1965) have described the finding, in the degenerated brain tissue of a patient who had died from progressive multifocal leucoencephalopathy, of more or less spherical particles arranged in crystalline aggregates resembling particles of the tumour-producing papova group of viruses. This finding is of particular interest, because the papova viruses have not yet been grown outside the body and in the absence of electronmicrography could probably not be demonstrated. If this observation is confirmed, it will add greatly to the plausibility of the latent virus explanation.

A variation of this theme is that the virus which causes the nervous lesions is not latent in the body, but gains access to it at about the time of vaccination. Numerous workers have recorded the occurrence of post-vaccinal encephalomyelitis in patients who were suffering from or exposed to respiratory disease (see Fyfe and Fleming 1943, Report 1959*a*).

(c) That it is a manifestation of what is usually called an auto-immune reaction, but which is more correctly referred to as an auto-allergic reaction. It is supposed that, in response to an antigen formed in the body, an antibody is produced having its main action directed against the myelin of the nerve sheaths. This view was put forward by Glanzmann (1927), supported by Finley (1938), and critically discussed by Hurst (1952). Schwentker and Rivers (1934) found that brain-specific antibodies could be produced experimentally by injection of rabbits with homologous brain tissue altered in some way, such as by autolysis, infection with vaccinia virus, or alcoholic extraction followed by combination with a foreign protein; the antigenicity of the white matter was much greater than that of the grey matter and paralleled the myelin content of the suspension used for injection.

Later workers, such as Kabat, Wolf and Bezer (1947, 1949), found it possible to set up in monkeys, and Thomas, Paterson and Smithwick (1950) in dogs, a demyelinating encephalitis by the injection of brain tissue combined with Freund's (see Freund *et al.* 1947) adjuvant. The antigenic substance responsible for stimulating the formation of the destructive antibody appears to be a lipoprotein (see Hurst 1953) or a phosphatide (Peers 1950); and it can be removed to a considerable extent by centrifugation (Hottle and Peers 1954). The experimental disease can be passively transferred to rats by transfused lymph node cells taken a few days before the disease is due to appear in the donor animal (Paterson 1960). In Humphrey and White's (1964*b*) opinion and in that of Alvord (1965), this and other evidence strongly favours the view that the experimental lesion depends on an allergic response to auto-antigens of nervous tissue and that a delayed type of hypersensitivity is the main cause of the lesions.

Working with rabbits Linz, Lecocq and Mandelbaum (1965) found that the subcutaneous injection of the white matter of human brain mixed with Freund's adjuvant (Kibler and Barnes 1962) caused paralysis in 78 per cent of animals, whereas plain rabbit cord mixed with adjuvant caused paralysis in only 21 per cent. But when the rabbit cord was incubated with *Streptococcus pyogenes* type 12 for two days it caused paralysis in 43 per cent. Staphylococci had no such effect. Though many of the animals formed precipitins to the injected antigen, no relation was found between the precipitin content of the serum and the development of encephalitis.

In man the incubation period of post-vaccinal encephalitis, namely 10 to 13 days after vaccination, fits in well with the auto-allergic explanation. By then the patient has acquired some degree of immunity and the antibody produced can react with the antigen in the brain tissue. The failure of infants under two years of age to suffer from a microglial demyelinating encephalomyelitis is explicable by the absence of myelin from the nerve sheaths during early post-natal life and the poorer antibody-forming ability of the newborn (see de Vries 1960).

Against the auto-allergic view is the difficulty of explaining the aggregation of cases in time and space (see Report 1959*a*). This would seem far more to favour the second view postulating the activation of a latent neurotropic virus or simultaneous infection from outside with such a virus. It may be, of course, that in the localized areas in which several cases have occurred at about the same time the population was inbred and that many families suffered from nervous instability including an allergic diathesis. In spite of this objection, the similarity of the disease to that which occurs naturally in variola, measles, and rubella, and artificially during anti-rabies vaccination, suggests that some general immunological mechanism is responsible rather than direct infection by a virus. (For a full discussion on experimental allergic encephalitis, see the proceedings of the special conference on the demyelinating diseases in Report 1965*a*.)

PROPHYLAXIS

Two specific measures have been suggested for preventing post-vaccination encephalomyelitis. Gispen, Lansberg and Nanning (1956) advocated the use of combined active and passive immunization against smallpox. They found that the injection of even 960 mg of antivaccinial gamma globulin did not interfere with the reaction to smallpox vaccine. In practice they recommended a dose of 320 mg of dry gamma globulin for this purpose. Six years later Nanning (1962) reported on the apparent success of this method. A controlled study on Dutch recruits had been

carried out in which one group received 2 ml of a 16 per cent solution of gamma globulin made from recently vaccinated subjects and the other group a placebo of gelatin glucose solution. In the first group of 53 630 recruits three cases of post-vaccinal encephalitis were reported: in the control group of 53 044 recruits thirteen cases were reported. After the beginning of May 1959 all recruits were given 2 ml of antivaccinial gamma globulin at the time of primary vaccination. During the following two years only one case of encephalitis was reported among 30 000 vaccinated subjects. This incidence was very much lower than that of 1 in 4000 prevailing before gamma globulin was introduced.

An alternative approach was made by Herrlich (1964), who suggested preliminary vaccination with a killed, preferably formolized, vaccine, so that neutralizing antibody should be present at the time of vaccination with the live virus. At the date of reporting he had followed up 91 000 persons vaccinated in this way and had met with only two cases of encephalitis, both of them mild. This, again, was a much lower incidence than that previously recorded in Germany of 1 in 2000 to 1 in 3000 primary vaccinations.

It is too early to say whether either of these methods will prove effective. The rationale of both of them depends on a specific antivaccinial effect, which is rather difficult to reconcile with our present conception of post-vaccinal encephalomyelitis as an allergic phenomenon. Herrlich, Ehrengut and Schleussing (1965*b*) criticized Nanning's results on a number of statistical grounds; and Schlüter (1964) reported that already two cases of post-vaccinal encephalitis had occurred in children after primary vaccination, in spite of their having previously been immunized with Herrlich's killed vaccine. Rohde (1964) reported a further case.

Of non-specific measures the most obvious one is to restrict primary vaccination to the first two years of life when the incidence of the disease—if indeed it occurs at all in its typical form at this age—is at a minimum. This is the course strongly advocated by Müller (1946) in Switzerland, and Berger and Puntigam (1954) in Austria, and in the official German report (1959*a*) and the British report (1963). The advantage of choosing the second rather than the first year has already been referred to. When primary vaccination has to be performed at a later age, then it is probably wise to ensure that the subject is healthy at the time, is not convalescent from an infectious disease, and has not recently been injected with a living vaccine such as that against yellow fever.

DISCUSSION AND SUMMARY

The aetiology of post-vaccinal encephalomyelitis still awaits a satisfactory explanation. The evidence points fairly strongly to an allergic basis. The fact that neurological complications occur most commonly after smallpox vaccination, rabies vaccination, and the injection of tetanus antiserum—all procedures in which a foreign protein is introduced into the body—suggests that the nervous system becomes sensitized and reacts accordingly (see Pette 1947). Why the complication should be limited to only a small proportion of those vaccinated presumably depends on the immunological reactivity of the individual, just as in other manifestations of allergy such as hay fever and asthma.

Whether on this basis it is possible to explain the undoubted aggregation of cases in time and place that have been noted is more difficult. Encephalomyelitis, histologically similar to that seen after vaccination, may occur as a complication of various infectious diseases, particularly measles, varicella and rubella, in which no foreign protein is

injected and in which the sensitizing antigen is presumably made in the body from damaged nervous tissue; and it may be that the local aggregation of post-vaccinal cases is occasioned by infection of the patient with another virus which activates the vaccinia virus and in subjects predisposed to allergy leads to the formation of an auto-antigen. There are many records of cases of post-vaccinal encephalomyelitis occurring in association with an infectious disease, but mere coincidence cannot be excluded. The failure to demonstrate an extraneous virus in the central nervous system need not be taken too seriously, because if the disease is a manifestation of allergy a minimal infection might well be sufficient. In anaphylaxis, for example, we know that even a minute quantity of serum is sometimes enough to cause sensitization.

Passing from speculation to fact, there can now be little doubt that post-vaccinal encephalomyelitis is closely associated with late primary vaccination. After the end of the second year of life the risk increases to reach a maximum apparently between 6 and 12 years of age, though it still remains high after this. Without discussing the policy of vaccination (see Dixon 1962), which falls outside the aim of this book, we may say that, if compulsory vaccination is to be imposed, the compulsory element should be limited to the first two, or at most three, years of life; and that, if voluntary vaccination is recommended in view of the fact that at least one-third of mankind lives in the midst of endemic smallpox and that transfer of infection to other countries is now so easy, then again the strongest emphasis should be laid on early vaccination, and on revaccination at fairly frequent intervals so as to maintain a reasonably high degree of immunity.

It may be mentioned that there seems to be little justification for the common practice of trying, by limiting the size of the vaccination site and the amount of vaccine inoculated, to induce only a mild reaction. Evidence that this has any effect in diminishing the risk of encephalomyelitis is lacking. Moreover, against this practice is the weighty evidence accumulated by Cameron at the Metropolitan Asylums Board Hospitals in 1902-4 (see Report 19286) and by others that the degree of immunity resulting from vaccination is in proportion to the area of scar tissue left. (For **a** review of post-vaccinal encephalomyelitis, see Herrlich, Ehrengut and Schleussing 1965*a*.)

OTHER DISEASES ASSOCIATED WITH VACCINATION

Various diseases of the respiratory and gastro-intestinal tract occur in infancy and it is not surprising that some of these should coincide with vaccinia. How far their course is influenced by the concurrent vaccinial disease, or how far vaccinia activates or provokes other infections, it is impossible to say, but reference may be made to the German report (1959*a*) and to the paper by Conybeare (1964).

What is of greater moment here is the cause of the not inconsiderable number of deaths that occur in infancy from disease apparently of the central nervous system. Little is known about these so-called encephalopathies, and until a systematic study of them is made from a clinical, epidemiological and pathological angle, the part played in their causation by vaccinia virus will remain unexplained.

16

ALLERGIC MANIFESTATIONS: COMPLICATIONS, INCLUDING NEUROPARALYSIS, AFTER RABIES VACCINE

NEXT TO SMALLPOX, antirabic vaccination is the oldest form of human vaccination and, like vaccination against smallpox, it has been attended by serious complications. Apart from local reactions at the site of injection, these have been almost entirely of the neuroparalytic type.

Local reactions

Allergic. Localized redness, swelling and pruritus at the site of the injections coming on between the 6th and 11th days are not uncommon (Cornwall 1919). They appear within a few hours, reach their maximum in 6-8 hours, and are usually gone by the next day. The erythema may spread over the abdominal wall, into which the injections are usually made, in the form of a scarlatiniform rash (Rernlinger 1927*b*). Urticaria, either local or general, may occur, particularly in children, or less often a papular eruption. A delayed reaction, resembling the tuberculin reaction, characterized by local redness, induration, tenderness, and itching, sometimes associated with low fever, headache, nausea, malaise, and enlargement of the lymph glands, may be seen (Horack 1939).

Suppuration. Abscess formation is uncommon, but does occur. It may be due to contamination of the syringe or of the vaccine. In corpulent patients in whom the vaccine is but slowly absorbed, deep chronic abscesses sometimes form. Vaccines prepared from the central nervous system of rabbits that have died in the night and been subject to post-mortem bacterial invasion are most likely to cause infection. At Warsaw 22 out of 40 patients vaccinated on one day in 1901 suffered from general streptococcal infection and four died. At Palermo two deaths occurred from cellulitis (Remlinger 1927*b*).

General reactions. General reactions are not uncommon after rabies vaccine made from duck eggs. Hildreth (1963) reported that 41 out of 1000 patients receiving this vaccine suffered from some sort of generalized reaction; 20 had urticaria with or without other symptoms of serum sickness and 21 had chills and fever. Kaiser, Sokol and Beall (1965) described three cases of acute abdominal pain, accompanied by nausea and vomiting, coming on within 2 to 15 minutes of the injection of 1 ml of duck embryo vaccine. Three similar cases were reported to the authors personally by Dr George Bracher of the Peace Corps in Hawaii. All recovered within 24 hours. It seems probable that these reactions were a manifestation of anaphylactic sensitivity to duck egg protein.

Neuroparalytic accidents after antirabies vaccination

It was not long after the pasteurian method of protecting against rabies was taken into routine use that attention was drawn to cases of neuroparalysis occurring during or just after the course of treatment. Little was said about them in print. Among the directors of the Pasteur Institutes

there was a conspiracy of silence, caused by a fear partly of bringing Pasteur's method into disrepute and partly of bringing blame upon themselves. Their position was not an easy one. Though little was acknowledged publicly, rumour was active and each fresh case furnished the occasion for local conversation and gossip. The poisonous atmosphere of covertly expressed criticism in which they moved reacted on the morale of the staff and made them miserable. What was to be done?

At Kharkov, said Zlatogoroff (see Remlinger 1927*a*), they found themselves faced by a terrible dilemma. When they used an intensive method of treatment, neuroparalytic accidents occurred. When they used a milder form of treatment, many of the patients contracted rabies.

It was realized sooner or later that nothing was to be gained by silence, and that the right course was to collect all the available information, scrutinize it carefully, and see what measures could be taken to meet the danger. At the first international conference on rabies at Paris in April 1927 the available figures were summarized by Remlinger (1927*a*). He had managed to collect records of 329 cases of neuroparalysis occurring among 1 164 264 persons treated, but he explained that this was certainly an underestimate and that the real figure probably lay between 500 and 1000.

A further series of cases was collected and analysed by Greenwood (1945-6) based on McKendrick's annual reports covering the years 1927 to 1939, but including some cases occurring during the years 1940 to 1944. Greenwood's series comprised 222 cases among 1 290 758 persons treated.

Apart from these two main series, numerous smaller series and individual cases have been reported by various observers. Table 8, which contains many of these, does not pretend to be complete, but it does add another 300 or more to the collected series of Remlinger and of Greenwood.

Inspection reveals great variability between the reports of different observers, the incidence rate ranging from 86 to 2367 per million vaccinated subjects. Part of this is probably due to the inclusion of small numbers of cases, and part to the great irregularity in their occurrence. Thus Schweinburg (1924), who reported on cases of neuroparalysis in patients treated at the Rabies Institute in Vienna, said that not a single case occurred among 6814 patients treated between 1894 and 1915, but that 35 cases occurred among 7875 patients treated between 1915 and 1924, even though between 1896 and 1921 the same strain of virus fixe and the same routine of inoculations were used. Again, Moftah and Nabih (1931) in Cairo had thirteen cases spread over many years without a single fatality, and then seven cases in one year all of which terminated fatally. (See also Aksel 1963.)

CLINICAL FORMS OF NEUROPARALYSIS

Neuroparalytic accidents take four clinical forms: (1) peripheral neuritis, (2) dorsolumbar myelitis, (3) acute ascending myelitis of the Landry type, and (4) encephalomyelitis. Of these, dorsolumbar myelitis is the commonest, encephalomyelitis coming next (Gupta, Mital, Agarwal and Arora 1964).

Peripheral neuritis usually affects one or more of the cranial nerves—facial, oculomotor, glossopharyngeal and vagus in this order—and is non-fatal.

TABLE 8. Neuroparalytic accidents of antirabic vaccination. Collected figures

Author	No. of patients treated	No. of accidents	Incubation period in days after 1st injection	Incidence per million patients treated
Appelbaum, Greenberg and Nelson (1953)	93 150	46	8–21	494
Greenwood (1945–6)	1 290 758	222	—	172
Herrmann (1926)	4063	5	—	1231
Koprowski and LeBell (1950)	3305	6	—	1815
Laha (1957)	2455	5	7–17	2037
Latimer, Webster and Gurdjian (1951)	113 484	40	8–10	354
McCoy (1930)	1800	4	6–20	2222
McFadzean and Choa (1953)	14 119	17	8–37	1203
Moftah and Nabih (1931)	27 060	20	—	739
Remlinger (1927*a*)	1 164 264	329	11–30	283
Remlinger (1952)	155 033	74	—	475
Report (1962*a*)	7213	4	7–14	555
Schweinburg (1924)	14 789	35	—	2367
Singh and Gupta (1964)	6000	11	8–18	1833
Smith (1931)	93 279	8	10	86
Stuart and Krikorian (1933)	9950	5	10–13	503
Udaondo, Sanguinetti and Zunino (1934)	10 626	25	14	2353
Pait and Pearson (1949)	5500	9	4–18	1636
Clément (1961)	73 417	14	9–21	191
Aksel (1963)	92 367	35	—	379
Total	3 353 916	972	—	2 (1 in 3448)

Dorsolumbar myelitis comes on usually during the second week of treatment or just after it. Premonitory symptoms are weakness, lassitude and fainting. The attack is ushered in by fever of varying degree, chilliness, pain in the back, tingling and weakness of the lower extremities, difficulty in micturition and defaecation; and it passes on to paralysis of the legs. Recovery sets in within a week or two and is often complete, but some patients are left with a disability, such as partial paralysis of the legs, difficulty in control of the bladder, or disturbances of sensation. The case-fatality rate is about 5 per cent. According to Gupta and Bhargava (1961) there are no sensory disturbances, but sphincter trouble is invariable.

In the acute ascending type of myelitis, referred to as the Landry type, the onset is more acute. The attack starts with high fever, headache, vomiting and severe pain in the dorsolumbar region. Paralysis of the legs rapidly sets in, together with retention of urine and constipation. During the following day or two the pains pass upwards to the thorax, and then on to the head and neck. The patient is paralysed from head to foot, and is unable to eat or drink or speak clearly. Just when death is expected from bulbar paralysis, recovery is apt to set in, and the patient finds the paralysis disappearing in the reverse order to that in which it came on. Some residual weakness may be experienced, and facial paralysis may persist long after other signs have vanished. Recovery, however, is by no

means assured; in fact, the case-fatality rate is generally given as 30 per cent.

The encephalomyelitic form is characterized by fever, disturbances of consciousness, and a variable amount of paralysis, often affecting the cranial nerves. Recovery is the rule, but about 5 per cent of the patients die.

Except in the peripheral neuritis form examination in the laboratory often reveals a blood leucocytosis, with a variable rise in the cellular and protein content of the cerebrospinal fluid. The Guillain-Barré type of polyradiculoneuritis is said to be rare. Bertrand, Duplessis and Diane (1965), who described one case, drew attention to the dissociation between the cell and the protein content of the cerebrospinal fluid. In their case the lymphocytes numbered one per cubic millimetre while the protein content was 1.50 g per cubic millimetre.

Histological examination of material removed at autopsy shows the presence of lesions in the grey and white matter of the cord. The ganglion cells of the grey matter exhibit all stages of degeneration from slight chromatolysis to complete necrosis. In the white matter there is perivascular cuffing together with demyelination and destruction of the axis cylinders. No Negri corpuscles are to be found, and injection of the brain into mice or rabbits does not give rise to rabies. The picture is similar to that of demyelinating encephalomyelitis seen as a complication in smallpox and measles and after various other forms of vaccination.

EPIDEMIOLOGICAL FEATURES

Reference to Table 8 shows considerable variation in the length of the *incubation period* dating from the first injection. According to Stuart and Krikorian (1933) 80 per cent of the cases come on during the first three weeks of treatment, and the remainder always within five weeks. Remlinger (1927*a*), however, quotes two cases occurring 62 and 69 days after the end of the course of treatment. The commonest time seems to be 10-17 days, that is to say towards the end of the standard 14-day course of treatment. Neither the incidence of paralysis nor the length of the incubation period bears any relation to the site, the severity or the date of the bite; they are determined solely by the vaccinal treatment (Stuart and Krikorian 1928).

The *case-fatality rate* is highest in the Landry type and lowest in the type characterized by peripheral neuritis. The average figure for all forms of paralysis given at the Rabies Conference in 1927 was 16.85 per cent (Remlinger 1927*a*). This figure may well be too high and refer mainly to the severer forms of paralysis which were treated in hospital. A figure of 10 per cent would probably be more realistic. But great variations exist; thus not a single death occurred among 46 patients in New York (Appelbaum, Greenberg and Nelson 1953), whereas seven out of seven consecutive patients died in Cairo (Moftah and Nabih 1931).

Adults are affected more than children, males more than females, brain workers more than manual labourers, and in the colonies Europeans more than the indigenous inhabitants (Remlinger 1927*a*, 1932, Stuart and Krikorian 1928). Those at the extremes of life suffer least (Gupta *et al.* 1964).

The incidence is highest among those treated with dried cord by Pasteur's or Högyes' method and lowest among those treated with carbolized, etherized or glycerolated vaccine as in such vaccines as those prepared by Fermi, Hempt, Semple, Alivisatos or Calmette (Stuart and Krikorian 1928, Smith 1931, Remlinger 1927*a*, 1952). Of these, the

Rabies Conference found Semple's carbolized vaccine to be the safest of all (Remlinger 1927*a*). Greenwood's (1945-6) analysis showed an incidence of paralysis of 110 per million persons treated with killed vaccines as against one of 343 per million persons treated with live vaccines, i.e. dried cord. Intensive treatment, in which cords dried for a shorter period than normal are used, or in which the intensified method of Högyes is employed, is said to carry a particularly high risk of paralytic accidents (Stuart and Krikorian 1928, Aksel 1963).

According to Appelbaum, Greenberg and Nelson (1953) one of the most important factors is the number of injections given. In their experience the incidence was five times as high in those that received fourteen injections as in those that received seven or fewer. In McFadzean and Choa's (1953) series of seventeen cases, all but two had had more than seven injections.

The incidence in patients treated at different institutes varies greatly. For example, at Coonoor it was 1 in 31 314 vaccinated patients, at Algiers 1 in 5389, at Saigon 1 in 5244, at Constantinople 1 in 3734, at Java 1 in 637, at Los Angeles 1 in 611, and at Shanghai 1 in 259 (Remlinger 1927*a*, Pait and Pearson 1949, Clément 1961). There is no simple explanation for this, since many institutes used the same method of preparation of the vaccine yet differed greatly in the number of accidents they observed.

It may be mentioned that neuroparalytic accidents are by no means uncommon in dogs vaccinated by the pasteurian method (Remlinger 1927*a*).

PATHOGENESIS

Various explanations have been put forward of the nature and mechanism of production of neuroparalysis. As has already been noted, some cases are undoubtedly due to virulent virus fixe in the vaccine. Some, according to Herrmann (1926), are psychogenic caused by the patient's intense fear of contracting rabies. A few are purely adventitious, having nothing whatever to do with the bite or the vaccine. But though both Remlinger (1927*a*) and Stuart and Krikorian (1928) oppose it, the opinion is now generally held that most neuroparalytic accidents are of anaphylactic origin. The basis for this is largely experimental work on animals.

Remlinger (1919) and Schweinburg (1924) were among the first to show that paralysis could be induced in animals by repeated subcutaneous injections of normal nerve substance. Schweinburg (1924) gave rabbits a series of 14 subcutaneous injections of normal human cord prepared in the same way as Pasteur's vaccine. All the animals lost weight from the start; and, after the course was over, 13 of the 69 rabbits injected suffered from flaccid paralysis and 9 died. On the other hand 56 rabbits treated by Högyes' method remained well. Since 5-10 times as much cord substance is injected by Pasteur's as by Högyes' method, Schweinburg concluded that, apart from individual differences in susceptibility of the animals, paralysis depended on the total amount of nerve substance injected.

Whether paralyses produced in this way are strictly analogous to those occurring in patients given antirabic treatment is perhaps open to doubt. Rabbits are apt to become paralysed after injection with a number of different substances, including those containing no nervous tissue. Hurst (1932), who injected rabbits subcutaneously or intramuscularly with normal brain tissue of the guinea-pig, sheep, monkey or man, observed severe toxic manifestations leading to emaciation and death. In a few animals paralyses occurred, but histological examination failed to reveal

any lesions in either the central or the peripheral nervous system, thus leaving the cause of the paralysis unexplained.

Stuart and Krikorian (1928) made extensive observations on rabbits and white rats. They were able to produce paralytic accidents by the repeated injection of nerve substance, normal or rabid, homologous or heterologous. The incidence of neuroparalysis could be greatly diminished by treatment of the brain with phenol.

Alvord (1949) gave guinea-pigs a single subcutaneous injection of brain or brain extract suspended in a mixture of light paraffin oil and killed tubercle bacilli in Falba. Paralysis was observed 2-10 weeks later. He regarded the responsible agent as a heat-stable phosphatide-like material present in the white matter of the central nervous system. Further experiments with Freund's adjuvant showed that the encephalitic factor present in rabid brain could be extracted with benzene or ether followed by washing in an aqueous solution of calcium acetate (Bell, Wright and Habel 1949).

Hottle and Peers (1954) were able to remove a great part of the encephalitogenic activity of infected rabbit brain without diminishing appreciably its protective power for mice. A 5 per cent suspension of brain tissue in distilled water was centrifuged for one hour at about 1000G, its encephalitogenic activity tested by a modification of the method of Freund, Stern and Pisani (1947), and its protective power by two intraperitoneal injections of vaccine followed by intracerebral inoculation of the challenge virus.

The production in dogs of lesions similar to those met with in the demyelinating encephalomyelitis of man was recorded by Carol-Dimitriu and Bercea (1964). They injected large and repeated doses of homologous or heterologous (sheep) brain, and found that normal brain was well tolerated, but that brain containing the virus fixe of rabies was not. Some of the dogs died without symptoms of paralysis, but in these animals and in the survivors which were killed congestion, haemorrhage, peri-vascular infiltration, diffuse or focal glial and neuronal lesions, and demyelination were observed on histological examination.

The allergic nature of paralytic accidents in man is supported by the findings of Horack (1939) and Koprowski and LeBell (1950). Horack analysed the history of sixteen patients who had suffered from neuroparalysis during antirabic treatment and found that 80 per cent of them had an allergic history as opposed to 30 per cent in a control series who had not suffered during treatment. Koprowski and LeBell (1950), studying 50 samples of serum from patients in New York who had been immunized with Semple's vaccine, found complement-fixing antibodies to a brain antigen in 17 out of 34 patients who had received a 14-day course but not in any of those who had received only a 7-day course of treatment. In two out of three patients who had suffered from encephalomyelitis during the course the titre of antibody was high, but not in the third patient. The inference is that antibodies specific for brain tissue are formed in response to the vaccine and react with the brain of the patient *in situ.*

In concluding this section it is interesting to refer to the discussion on pathogenesis by Remlinger in 1927 (1927*a*). He considered ten possible causes and failed to reach any conclusion. He ruled out an anaphylactic origin on his failure to reproduce paralysis in dogs, guinea-pigs and rabbits by the intracerebral injection of nervous tissue; on the absence of neuroparalytic accidents among patients suffering from various diseases, especially neurasthenia, who were being treated by the subcutaneous injection of normal nervous tissue; on the apparent innocuity of the

Russian practice of giving two separate courses of antirabic treatment, separated by 2 to 4 weeks, to patients who had received particularly severe bites; and on the absence of neuroparalysis among patients who had been bitten on two or three occasions and had had a course of treatment each time.

None of these objections carries much weight. Though Remlinger (1927*a*) failed to induce paralysis in his animals by Besredka's method of intracerebral injection of nervous substance, he did do so when he injected rabbits intramuscularly with two or three doses of rabbit brain containing active or inactivated virus fixe (Remlinger 1919). The other three objections can probably be disposed of on statistical grounds. If, as indicated in Table 8, the average incidence of neuroparalysis is of the order of 1 in 3500 vaccinated patients, then, in view of the probably small numbers included in Remlinger's last three categories, the absence by chance alone of any accident is not surprising. Incidentally it may be mentioned that in one of the five cases of neuroparalysis seen by Laha (1957) the patient had received antirabic treatment 27 years previously, and that in the two cases seen by Latimer, Webster and Gurdjian (1951) both had a history of previous antirabic treatment.

Though the evidence is not conclusive, most workers nowadays probably regard neuroparalytic accidents during antirabic treatment as examples of allergy. This is the only explanation so far advanced, supported as it is by animal experiments and by antibody studies in man, that offers satisfaction and that fits in with the observations on the occasional occurrence of encephalomyelitis during other forms of vaccination. (For further references to neuroparalytic complications of rabies vaccination, see Huguenin and Bianchi 1963.)

PROPHYLAXIS

It was hoped that the use of duck instead of rabbit vaccine would eliminate the occurrence of paralytic accidents, but this hope has proved unfounded (Prussin and Katabi 1964). According to Hildreth (1963) two well-documented and two less well-documented cases of 'neurological abnormalities' are known to have occurred during or shortly after treatment with this vaccine (see also Kaiser, Sokol and Beall 1965).

A more promising method is described by Svet-Moldavskij and his colleagues (1965) in the Soviet Union. These workers believe that neuroparalytic accidents are due to (1) an encephalitogenic collagen-like protein present in the adult brain, (2) additional enhancing factors, and (3) the immunological reactivity of the vaccinated person. One of the enhancing factors is bacterial infection or contamination of the vaccine, caused either by the use of infected animals or by imperfect processing. The contaminants act like Freund's adjuvant, though more weakly. Most important, however, is the finding that the brain of the rat does not become encephalitogenic till the 18th day after birth, as judged by the failure to produce neuroparalysis in guinea-pigs by subcutaneous injection of a suspension of brain tissue mixed with an equal quantity of Freund's adjuvant. Vaccine is therefore being made from the brain of suckling rats infected with virus fixe at 4-8 days of age and killed 3-4 days later when moribund. Over 9500 persons have been injected with this vaccine without a single neuroparalytic accident.

VALUE OF ANTIRABIC VACCINATION

The rationale of antirabic treatment is easy to understand, but the mechanism by which a dead vaccine given after the introduction into the body of a living virulent virus is able to prevent the development of rabies is very puzzling. This is not the place to discuss the subject, but it is well to recall that probably only 5-15 per cent of patients bitten by a rabid animal are likely to contract the disease when left untreated (see Knowles 1928). On this basis Appelbaum, Greenberg and Nelson (1953) calculate that, in New York City between 1935 and 1948, of the 707 persons bitten by rabid animals 35 to 106 would have contracted rabies had they been left untreated. In fact only six cases occurred, and only two of these had been vaccinated, so that antirabic vaccination can be credited with having saved 33 to 104 lives.

If the average risk of a neuroparalytic accident is but 1 in 3500, then it is far smaller than the risk of contracting rabies. It is sufficiently high, however, to insist on limiting vaccination as far as possible to persons who have been bitten by an undoubtedly rabid animal or at any rate have an open skin lesion contaminated by the saliva of such an animal. Not only is vaccination inadvisable after a plain scratch or after licking of the intact skin, but it should seldom be advised unless there is strong evidence to believe that the animal was suffering from or was in the incubation period of rabies at the time of the attack. Herrmann (1926) draws attention to the tragedy of rabies developing in vaccinated persons who have never come into contact with street virus but who have been injected with a cord suspension containing insufficiently attenuated fixed virus; and Remlinger (1932) to the tragedy of neuroparalysis in vaccinated persons who have been bitten by non-rabid animals.

When no information is available about the state of the animal, the question whether to vaccinate or not to vaccinate is a very difficult one. Numerous factors must be taken into consideration, such as the species of animal, the local prevalence of rabies in that species, the nature, site, and severity of the bite, the degree of contact of the skin with the animal's saliva, the age, sex, and allergic history of the patient and so on. If it is decided to vaccinate in a doubtful case, then it is probably wise to give a dose of antirabic serum followed by a short course—not more than seven injections—of antirabic vaccine. In this way the risk of neuroparalysis should be greatly lessened. It may be worth while, as Horack (1939) advises, to test the patient for allergy to the vaccine and, if it is present, to attempt desensitization by repeated injections every 15 minutes with increasing strengths of vaccine, beginning at a 1/1000 dilution and working up till the undiluted vaccine can be injected without causing a reaction.

17

ALLERGIC MANIFESTATIONS: ENCEPHALOMYELITIS AFTER OTHER VACCINES

Typhoid fever vaccine

THE FIRST REPORT on nervous disturbances following vaccination against typhoid fever appears to have been made by Gubb (1915) in Britain; but it was not till the end of the first world war that serious attention was drawn to the subject by a group of French workers.

Gubb's case was not very convincing. Immediately after a single dose of antityphoid vaccine a soldier, aged 48 years, began to suffer from obstinate constipation. About eight months later he had trouble with micturition, which proceeded to incontinence. The patellar reflexes were found to be completely abolished. Gubb regarded these disturbances as due to toxaemia affecting the lumbodorsal centres.

In 1919 a number of reports appeared in the French medical press. Roussy and Cornil (1919) and Roussy (1919) each described one case, and Souques (1919) described seven cases of what might perhaps be called cortical thrombosis (see Bury 1920). In these cases nervous symptoms appeared within 24 hours of injection.

The patient seen by Roussy (1919) lost consciousness and fell. He was taken to hospital where he was found to have a right hemiplegia, aphasia and some meningeal symptoms, probably the result of softening in the left peri-rolandic area caused by thrombosis or embolism. In the case reported by Roussy and Cornil (1919) the patient had a heavy feeling in his left arm the day after injection and difficulty in moving the hand. When examined four years later he had athetosis and incoordination of movement in the left hand with serious changes in the sensory system of the hand and forearm and motor ataxia. Two of Souques' (1919) patients suffered from a persistent right hemiplegia. Four of them exhibited symptoms such as intense headache, vomiting, amnesia, fits, and change of character; the seventh, after a severe reaction, had a swelling of the right half of the neck which passed on to exophthalmic goitre.

At the same time Guillain and Barré (1919) and Léri and Boivin (1919) each reported a case of Landry's acute ascending myelitis. In Guillain and Barré's case numbness and stiffness became apparent in the patient's legs the day after injection and the following day in his hands. Paralysis gradually came on and by the 9th day was complete in the legs, arms and face. Bulbar symptoms developed on the 7th day, and on the 10th day the patient died. No histological examination of the central nervous system was made at post-mortem. Léri and Boivin's patient first experienced tingling and numbness of the left foot eight days after injection. The following day he had similar symptoms in the right foot and the fingers, the next day weakness of the legs and rapidly developing flaccid paralysis passing upwards to the arms and neck. Paralysis reached its maximum in a fortnight, remained stationary for another fortnight, and then gradually disappeared.

Preti (1919) described two cases in soldiers. In the first the patient had a severe reaction after a single dose of typhoid vaccine with fever lasting for over a week. On the third night he woke up to find himself blind. This

persisted for ten days or so, after which he partly regained his sight. When examined six months later he was diagnosed as having suffered from optic neuritis followed by partial atrophy. The patient, who was 30 years old, was a non-smoker, non-drinker and had a negative Wassermann reaction.

In the second case a 19-year-old soldier had a violent constitutional reaction lasting four days after the second dose of a vaccine containing typhoid and paratyphoid bacilli. A fortnight later he experienced convulsive attacks of the left arm and face. These recurred very frequently. On one occasion the convulsions became generalized and were accompanied by trismus, secretion of bloody saliva, abolition of the cranial reflexes, and loss of consciousness. When examined a year later, he was suffering from frequent convulsions of the left arm with some motor weakness, probably due to irritation of an area in the right rolandic zone.

After attention had been drawn to post-vaccinal disturbances of the nervous system, several further cases were reported. Bury (1920) described a case in which incoordination affected the arm and leg muscles associated with some flaccid paralysis; the gait was ataxic, the pupils were unequal, and the whole picture was suggestive of tabes dorsalis; serological examination, however, of the blood serum and cerebrospinal fluid revealed no evidence of syphilis. Alajouanine, Fribourg-Blanc and Gauthier (1928) described a case of persistent paresis of the left leg, associated with temporary incontinence of urine; Gayle and Bowen (1933) a slowly developing but nevertheless fatal case of Landry's paralysis; Noïca (1932) three cases exhibiting partial or complete paralysis of one or more limbs, associated in one case with hemianopsia, aphonia, and deafness in the right ear; Benon (1924) a case of incoordination of the legs leading to a staggering gait; Giffin, Rogers and Kernohan (1948) a fatal case of hemiplegia in which post-mortem examination showed lesions ranging from oligodendral proliferation in the baso-frontal region to widespread and complete demyelination in the right occipital lobe with perivascular collections of large fat-laden phagocytes in the softened areas; and Putnam (1943) a case of acute paraplegia. Two further, unreported, cases may be referred to that were brought to the attention of the Ministry of Health in 1941 and 1942: one of general weakness, inability to sit up or walk, dyspnoea, collapse, and death from encephalomyelitis eight days after the injection; the other of fever, headache, nausea, delirium, convulsions, coma and death in 26 days with areas of haemorrhage and haemorrhagic necrosis in the brain at post-mortem.

Miller and Stanton (1954), who reviewed the cases of neurological sequelae of prophylactic inoculation, collected records of 10 cases of myelitis of the transverse or ascending Landry type after TAB vaccination and 20 cases in which various manifestations of cerebral or meningeal disturbance were observed.

In addition to organic nervous disease, vaccination against typhoid fever is sometimes followed by functional disturbances of which asthenia and general nervous depression are among the commonest. The symptoms may disappear in 2 or 3 weeks or last for months. In some cases they pass on to mania or to motor irregularities affecting standing and walking. Benon's (1924) case may have been one of these; indeed the patient recovered completely and went on to win the Croix de Guerre.

Some of the patients referred to had been injected with typhoid vaccine, but most with typhoid-paratyphoid (TAB) vaccine. In two of them, at least, symptoms came on after the first injection; in several of

them after the 2nd, 3rd or 4th injection; and in one or two of them after reinforcing injections. As a rule the incubation period was less than 24 hours, though in a few patients it was a week or more.

In two or three of the cases it looks rather as if the vaccine had activated a latent or incipient disease such as multiple sclerosis. Such an explanation, however, would not hold for the majority of cases; and it must be concluded that the vaccine was responsible, whether through allergy on the part of the patient or by some other mechanism, for causing disease of the central nervous system.

So few histopathological examinations have been made of fatal cases that little is known about the nervous lesions produced, but the scanty evidence available suggests that the encephalomyelitis is of the demyelinating type, similar to that seen after smallpox and rabies vaccination.

Whooping-cough vaccine

Madsen (1933) was the first to report a fatal case of encephalopathy after whooping-cough vaccine. A newborn infant was given two subcutaneous injections within the first week of life. Half an hour after the second injection it was seized with convulsions and died within a few minutes. In another case a premature infant vaccinated twice in the second week of life died suddenly without convulsions two hours after the second injection. During the next few years sporadic cases of convulsions after pertussis vaccine were recorded by various workers such as Doull, Shibley and McClelland (1936) and Taylor (1938) (see Miller and Stanton 1954, Cockburn 1958). Among these was a remarkable case recorded by Brody and Sorley (1947) of an infant that was vaccinated during what may have been an unrecognized attack of whooping-cough, suffered two weeks later from mild encephalitis; was vaccinated a second time and had an exacerbation one week later; was vaccinated for a third time and had an exacerbation three days later; and, after a spontaneous exacerbation about a year later, was given an intradermal test dose of vaccine which led within 12 hours to an attack of severe flaccid paralysis terminated seven weeks later by a fatal broncho-pneumonia.

It was not, however, till the report of Byers and Moll in 1948 that serious attention was drawn to the nervous complications of this form of vaccination. Byers and Moll collected records of 15 cases admitted to the Children's Hospital in Boston during the previous ten years. All the cases were in infants aged 5 to 18 months. None had a history of convulsions. The reactions occurred indifferently after the first, second or third injection, and came on within 20 minutes to 72 hours—mostly 18 hours. The outstanding symptom of the reaction was convulsions, lasting from a few minutes to several days. Changes in consciousness from drowsiness to deep coma followed in all cases. The duration of the acute illness was from 36 hours to 10 days. Of the 15 infants, two died of pneumonia, five had hemiplegia, two became virtually decerebrate, five suffered from mental retardation, regression or other nervous disturbance, and only one recovered completely.

Globus and Kohn (1949) reported on two cases, one of which was fatal. Death occurred four weeks after the second injection and at post-mortem widespread, almost massive, disintegration of the brain was seen. Toomey (1949) in the United States, who wrote round to a number of physicians, learned of 38 cases of severe reactions, mostly convulsions, after pertussis vaccine, of which two at least were fatal and twelve at least

showed irreversible changes of the nervous system. In England Anderson and Morris (1950) described a case of convulsions in a boy of two coming on 36 hours after the first injection of diphtheria-pertussis vaccine; eight months later there was dilatation of the left ventricle and diminished activity of the left cerebral hemisphere, and a year later mental retardation.

In 1953 Kong collected from the literature 82 cases of cerebral reactions after pertussis vaccination. Nearly all were in infants. Eleven of them proved fatal, usually in the acute stage; 24 were left with irreparable damage in the form of epileptiform convulsions, spastic paralyses, mental retardation, or change in character; in some cases the symptoms slowly retrogressed, and in 15 complete recovery occurred; in the remaining 32 cases full information was not available. Kong added another two cases of his own, and in 1958 Berg reviewed a total of 107 cases reported in the literature including those of Kong. Eight of the cases were fatal within 48 hours. In the whole series the fatality rate was estimated to be about 15 per cent, the persisting morbidity rate about 30 per cent, and the recovery rate about 50 per cent.

According to private information a doctor in the United States sent out 104 questionnaires to university and state health departments asking for information on reactions to pertussis vaccine between 1955 and 1960. Seventy-five replies were received. Of these fourteen contained reports of a total of 21 cerebral complications—15 of them in infants under one year of age, 17 occurring after triple vaccine, 3 after quadruple vaccine, and 1 after pertussis vaccine alone. Permanent mental damage or the continuance of convulsions was observed in 14 of the patients. Three patients recovered completely, and in four the outcome was not known.

Thursby-Pelham and Giles (1958) recalled having seen six patients during the previous ten years who had suffered from neurological reactions within 24 hours of pertussis immunization. One of the patients died and three were left with permanent brain damage.

In Sweden Strom (1960) stated that a nationwide investigation had revealed the occurrence of 36 cases of neurological complications after pertussis vaccination of about 215 000 children during the years 1955-8. Most of the affected children had convulsions, four died, and nine suffered from a severe encephalopathy. These figures were challenged by Malmgren, Vahlquist and Zetterstrom (1960), who reduced the number of genuine cases to four or five, giving an incidence of about 1/50 000 instead of Strom's 1/6000. In Germany Paschlau (1965) reported that no neurological complications were seen among 28 661 children injected with pertussis vaccine at Stuttgart between 1955 and 1963.

In England and Wales the Ministry of Health have records for the period 1958 to 1965 of seven fatal cases of encephalitis, meningo-encephalitis or encephalopathy after triple or quadruple vaccine containing pertussis bacilli as one of the components.

DISCUSSION

Briefly it may be said that disturbances of the nervous system after pertussis vaccine come on mainly within 24 hours, though sometimes they are delayed for 2 or 3 days. Clinically Hellström (1962) recognizes three types: (a) short seizures, that is to say convulsions without sequelae; (b) an encephalitis-like syndrome of unconsciousness, prolonged seizures, a high proportion of persistent neurological complications, and occasionally death; and (c) slowly progressive mental deterioration with or without convulsions having the character of infantile spasms. These manifestations are confined almost entirely to infants. Boys suffer more than girls. No

constant relation seems to exist between the occurrence of convulsions and the nature of the vaccine used—simple, alum-precipitated, or mixed; the size of the dose used; the number of the injection, though Berg (1958) says that most come on after the first; or the length of the interval between injections.

Opinion differs on the frequency of a history of previous convulsions or of nervous instability in the family. Toomey (1949) and Köng (1953) were both impressed with such a history, whereas Byers and Moll (1948) and Berg (1958) could find little or no evidence to suggest that the infants were in any way abnormal. The incidence is difficult to gauge and reports are contradictory. It must depend to some extent on the age of the infant and possibly on its state of health at the time of injection. Kong (1948) counsels against immunizing any child which has a history of convulsions or allergy, or of nervous or allergic disease in the family, is in poor general health, is suffering from an infectious disease, or has reacted strongly to a previous injection of pertussis vaccine.

It may be because these injunctions were complied with that not more trouble was experienced during the long series of pertussis vaccine trials carried out by the Medical Research Council in England and Wales (Report 1951, 1956*b*, 1959*c*). Altogether 18 children out of 57 000 vaccinated had convulsions within 72 hours, that is an incidence of about 1 in 3000. Cockburn (1958) argued that this was no more than the number to be expected among unvaccinated children of the same age; and to support his case he showed that the proportion of children that had convulsions within this period was hardly any higher than that of children whose convulsions did not begin till 4 to 28 days after injection, at a time when pertussis immunization could presumably not be blamed for them. Though none of the vaccinated children that had convulsions appeared to suffer from any serious persistent damage, the fact that about 1 in 3000 of them experienced convulsions within 72 hours shows that Strom's estimated incidence of 1 in 6000 was by no means necessarily exaggerated. So far as other figures are concerned, probably those of Berg (1958), based on 107 cases in the literature and already quoted, are as reliable as any, namely a fatality rate of about 15 per cent, a persisting morbidity rate of about 30 per cent, and a recovery rate of about 50 per cent.

The resemblance of post-vaccinal nervous disturbances to those seen in whooping-cough itself is very close. Byers and Moll (1948), for example, during their inquiry at Boston reported that 26 children were admitted to hospital suffering from the acute or chronic effects of encephalopathy coming on during an attack of the disease. Of these, seven died, ten were left with permanent nervous damage, three could not be traced, and six recovered. Levy and Perry (1948), working in two institutions in Washington state, found 20 children who were intellectually retarded as the result of this disease; eight were classed as idiots, eight as imbeciles, and four as low-grade morons. Taking a group of 128 children, including these 20, that had had their attack before two years of age, they found that 29.2 per cent showed intellectual retardation. The corresponding proportion for those whose attack occurred between 2 and 5 years was 14.3 per cent, and for those who were older 2.2 per cent.

Unfortunately nothing is known about the histopathology of encephalitis following pertussis vaccination, and it is therefore impossible to say whether it is the same as in the encephalitis of whooping-cough.

van der Horst (1950) regards the encephalitis of whooping-cough as a very special form of encephalitis; it is different both clinically and histologically from the demyelinating form that occurs as a complication

in smallpox, measles, varicella or after vaccination against smallpox. The white matter is spared; there is no perivascular microglial proliferation; and there is no demyelination. On the other hand, there is dilatation of the vessels in the meninges and the cerebrum with capillary haemorrhages; diffuse neuroglial infiltration of the grey matter; some perivascular infiltration with plasma cells and lymphocytes; and vacuolar degeneration of the ganglion cells. Miller, Stanton and Gibbons (1956) consider that the cerebral changes occurring during whooping-cough are those of an acute vascular encephalopathy, possibly anoxic in origin.

Miller and Stanton (1954) who review the whole subject of neurological sequelae to prophylactic inoculation, make the acute remark that pertussis vaccination stands alone in giving rise only to central complications, not to the myelitis or neuritis that are seen after other vaccines and administration of serum. This peculiarity, taken together with the very short incubation period, the frequent occurrence of convulsions after the first dose of vaccine in a young infant, and the high proportion of patients having persistent cerebral damage, does suggest that the mechanism of production is different from that of the demyelinating type of encephalitis, though occasional cases, such as that described by Brody and Sorley (1947), may well be of the allergic type.

In this connexion it is interesting to note that Levine and Wenk (1965) were apparently successful in reproducing an acute form of encephalomyelitis in rats by injecting them intra-peritoneally with a suspension of rat or guinea-pig spinal cord mixed with commercial pertussis vaccine. Paralysis of the limbs progressing to quadriplegia came on in 6-11 days, followed by death 1-2 days later. Post-mortem examination revealed extensive perivascular lesions in the central nervous system with enormous numbers of polymorphonuclear leucocytes and demyelination around the vessels. There is nothing, however, in these experiments to prove that pertussis vaccine was playing a specific role; other substances may have the same effect when mixed with brain tissue (see p. 173); nor is there anything to prove that the experimental disease in rats is similar to the disease that follows pertussis vaccination in man.

Though the histopathology of post-vaccinal encephalitis is obscure, the clinical manifestations are the same as those in the encephalitis of whooping-cough. It is not unreasonable to suggest that the cerebral disease in each instance results from the direct action of the toxin of the whooping-cough bacillus, van der Horst (1950), however, who considers this possibility, rules it out on the ground that the symptoms are too sudden in their onset and too severe to be accounted for by the direct action of a toxin. He thinks it more probable that the disease has an allergic basis.

Diphtheria toxoid

Though diphtheria toxoid, particularly in its alum-precipitated form, has often been responsible for provocation poliomyelitis (see p. 270), it has seldom been associated with disease of the central nervous system. During the second world war a few cases after the injection of APT were reported to the Ministry of Health. One child, aged 6 years, suffered from headache, irritability, and rigidity of the neck and died in two days; postmortem examination revealed the presence of encephalitis. In two other children bilateral retrobulbar optic neuritis developed, associated in one case with disseminated encephalomyelitis.

Stillerman (1948) in the United States reported a case of aseptic meningitis in a nurse coming on 2—3 days after the third dose of diphtheria toxoid. She recovered in about a week.

Miller and Stanton (1954) describe a remarkable case of acute bulbar encephalopathy after schick-testing in a boy often years who had previously been immunized against diphtheria. He was left with residual wasting of the left masseter and temporal muscles leading to difficulty in moving the jaw.

Poliomyelitis vaccine

Bojinov and his colleagues (1964) report 13 cases of neurological complications of Sabin's vaccine among a total of six million persons receiving the vaccine. The patients were mainly children of 9 years or over, but there were two adults among them of 30 and 32 years. Complications came on 2-20 days, mostly 7 days, after vaccination. The cases comprised one of the Landry type of polyradiculoneuritis, one of meningo-myelo-polyradiculoneuritis with paraplegia of the legs and meningitis, one of polyradiculoneuritis of the Guillain-Barré type, one of paresis of the left foot, three of polyneuritis affecting particularly the lower limbs, and six of neuritis with paresis of one foot. One of the patients died. Whether these neurological sequelae were related to the vaccine, or, in view of their rarity—1/500 000—were merely coincidental, it is impossible to say.

Bigi and Pazzagli (1965) also report on neurological disorders occurring after the use of Sabin's vaccine, usually within two weeks. In five children aged 8 to 14 years whom they observed, one had a transitory ophthalmoplegia, two an acute psychosis, and two general convulsions. Two of the patients, it may be noted, had suffered from previous neurological disorders. The authors admit the impossibility of proving cause and effect.

Webb and Smith (1964) are of the opinion that neuroparalytic accidents after poliomyelitis vaccine are due to antigen-antibody reactions occurring in the brain. The virus appears to gain access to the central nervous system during the viraemic phase, and antibody becomes detectable at the time when the virus is multiplying vigorously in the brain and cord. If the antibody reaches the central nervous system at some critical time in relation to virus multiplication, antigen-antibody reactions occur which may be associated with an inflammatory response. This may be manifested as an encephalomyelitis, or perhaps by long-term changes such as demyelination.

It is very doubtful, however, whether Sabin's vaccine gives rise to neurological complications at all. Certainly much stronger evidence will have to be brought than is at present available before their occurrence can be substantiated.

Yellow fever vaccine

The encephalitis that is occasionally seen after yellow fever vaccine appears to be due to the inherent infectivity of the virus rather than to an allergic reaction on the part of the patient and is therefore considered in Chapter 4.

Measles vaccine

Pestri (1966) reports one case of encephalitis in a child aged 14 months coming on eleven days after the injection of measles vaccine made up with

the attenuated living strain of Schwarz. Twitching was first noticed on the left side of the child's face, followed by fever, a tremor in the left hand, refusal to eat, and semi-consciousness. Fifteen days after the injection she had a temperature of 103°F, a left-sided hemiparesis, and appeared lethargic and very ill. The fontanelle was bulging slightly; there was involuntary myoclonic fibrillation of the fingers of the left hand and flaccidity of the left arm and leg with diminution of the reflexes. During her stay in hospital she had frequent severe epileptiform attacks. She was discharged after four months still suffering from left-sided hemiparesis and with questionable mental functioning.

GENERAL CONCLUSIONS

It is clear that encephalitis may follow vaccination against various diseases, and even the injection of serum (see Chapter 18). It occurs most commonly after smallpox and rabies vaccination. The term 'encephalitis', however, covers at least three or four different pathological pictures.

First of all is the perivenous microglial demyelinating form seen most characteristically after smallpox vaccination in children and adults.

Secondly is the encephalopathy occurring after smallpox vaccination in infants under two years of age, heterogeneous in its manifestations, and characterized particularly by meningeal and vascular lesions.

Thirdly comes the acute viraemic encephalitis seen most typically after yellow fever vaccination.

And fourthly perhaps a form, whose aetiology is entirely obscure, occurring after immunization against pertussis. Though the histopathology of this form is still doubtful it seems probable that the lesions are similar to those of the encephalitis which occurs as a complication of the natural disease whooping cough. If this is so, then the cerebral complications of pertussis vaccination differ from those following vaccination against smallpox, rabies or typhoid fever, just as the encephalitis that occurs naturally in whooping-cough differs from that seen in smallpox, rabies, measles or varicella. Possibly the encephalitis following pertussis immunization, confined as it is almost entirely to infants, should be classed with the infantile encephalopathies, but it presents a peculiar and fairly homogeneous picture which, as already pointed out, seems to distinguish it from both the demyelinating type of encephalitis and the heterogeneous encephalopathic manifestations of infancy. It may be a toxic rather than an inflammatory or allergic type of encephalitis. Much more work, however, will have to be done, especially in the histopathological field, on the various forms of encephalitic lesions met with in different diseases and after the use of various vaccines before a satisfactory classification can be advanced.

18

ALLERGIC MANIFESTATIONS: SERUM ENCEPHALOMYELITIS

THE NOT infrequent occurrence of neuritis after the administration of serum has already been described (pp. 144-56). The much less frequent occurrence of encephalitis or myelitis may be briefly referred to here.

In his review of serum sickness and anaphylaxis in 1942 Kojis was able to trace only four cases in the literature in which the central nervous system was affected after parenteral, as opposed to intraspinal, injection of serum with resulting paralytic disease. One of these, a case described by Morichau-Beauchant and Fagart (1924), proved fatal. It was in a man of 54 who received 10 ml of tetanus antiserum after a wound of the left knee. Thirteen days later he suffered from severe generalized urticaria, vertigo and vomiting. Two days later he had some difficulty in moving his legs; and the following day there was partial motor paresis, respiratory embarrassment, continuation of vomiting, and death; no post-mortem examination was made.

The other three cases are those described by Lerond (1926), Kennedy (1929), and Bourguignon (1931). Lerond's case was one of Landry's paralysis coming on 12 days after a prophylactic injection of tetanus antiserum, leading to paralysis of all four limbs and of the face, and just not proving fatal. Kennedy's patient was a boy who suffered from severe meningismus, bilateral swelling of the optic discs, aphasia, and partial right hemiplegia after prophylactic injection with scarlet fever antiserum; recovery occurred in about a month. The case described by Bourguignon was that of a boy aged eight years who was given a prophylactic dose of tetanus antiserum after a wound. Eleven days after the injection he had a serum reaction consisting of fever and urticaria, followed in a few hours by meningeal symptoms—painful stiffness of the neck, vomiting, strabismus, and a positive Kernig sign. Next day his right arm was totally paralysed; the following day his left arm was partly paralysed; and four days later there was paresis of both lower limbs. Recovery eventually took place and within three years the strabismus had disappeared.

In addition to these should be mentioned three cases of optic neuritis—two of them quite mild—coming on after pneumococcal (2) and meningococcal (1) antiserum described by Mason (1922); one of left-sided amblyopia and papilloedema reported by Bourrat (1929) after tetanus antiserum; and four cases reported by Allen (1931) characterized by such symptoms as hemiparesis, papilloedema, amblyopia, aphasia, alexia, and meningismus.

An unusual case of pseudotabes was described by Babonneix (1924) in a young woman who was given two subcutaneous injections of streptococcal antiserum at an interval of two days. Thirteen days after the first injection nervous symptoms appeared: general pains, numbness and formication affecting predominantly the lower limbs, loss of postural sense, ataxia, retention of urine, and complete abolition of all tendon reflexes. Six months later ataxia was still incapacitating.

Another case, described by Winkelman and Gotten (1935), was in a woman who was given two injections on the same day of normal horse serum to control bleeding from a tooth socket. She contracted a respiratory

infection, suffered from paralysis of the legs and died three days later. Post-mortem examination showed the presence of disseminated encephalomyelitis without demyelination.

Since Kojis' review cases have been reported by various workers. Elsässer (1942), in an analysis of 120 cases of post-serum polyneuritis, found that in 15 of them the central nervous system was affected and in 17 the cranial nerves were involved. Elsässer's cases included some of those just described. Csermely (1950) described a case in a man of 35 who suffered from generalized urticaria three days after an injection of tetanus antiserum. This was followed by malaise, headache, pain in the back, general weakness, and extreme hyperaesthesia of the skin, and on the 10th day by a right-sided hemiplegia and loss of consciousness. The cerebrospinal fluid was under pressure and contained 150 cells per cmm, mainly lymphocytes. The patient died four days later. At post-mortem soft yellowish foci enclosing large numbers of punctate haemorrhages were found in the left parietal lobe, and on histological examination perivascular demyelination was conspicuous.

Park and Richardson (1953) reported one case of mild encephalopathy after tetanus antiserum and two fatal cases of focal cerebral injury—the rarest complication of all—both with hemiplegia. Another case of focal encephalopathy was described in a woman by Poser (1957) coming on eight days after injection of tetanus antiserum and characterized by weakness and paraesthesia of the left arm and leg, drowsiness, lethargy, slurred speech, disorientation and retention of urine indicative of a focal lesion in the right frontal lobe in addition to generalized encephalomyelitis. She began to improve in 2 to 3 weeks.

Toogood (1960) records the development of coma in a man eight days after an injection of tetanus antiserum followed by death five days later. The patient was febrile, and had sustained clonus. At post-mortem an acute haemorrhagic leucoencephalitis was found.

In a case described by Williams and Chafee (1961) a boy who had contracted tetanus after a wound was treated with repeated doses of antiserum. The tetanic spasms ceased after seven days, but were followed the next day by urticaria and three days later by coma. Death occurred 13 days after the onset of tetanus, and histological examination revealed numerous pinpoint lesions of perivascular demyelination in the white matter of the brain.

A fatal case of acute disseminated encephalomyelitis and haemorrhagic leucoencephalitis was recorded by Miller and Ramsden (1962) in a girl who was given tetanus antiserum after a motor-bicycle accident. Fifteen days later neurological symptoms appeared and death followed in another nine days. Post-mortem examination showed extensive lesions in the brain and acute necrosis of the cord. Perivascular demyelination and cellular infiltration were found in the brain with confluent demyelination of the medulla. It is interesting to note that perivascular demyelination is described by Baker (1942) as a finding in cases of fatal tetanus.

There is another group of cases referred to by Young (1932). In these, the history is of a patient who receives antiserum, generally by the spinal route, in repeated doses. Three days to a month later he is given another dose. This precipitates a severe reaction manifested by generalized urticaria, followed in a few hours by convulsions, opisthotonos, coma, rapid irregular pulse, irregular breathing, and sometimes death. If the cord is affected, there is residual paralysis and muscular atrophy. Five out of seven of Young's cases of cerebral disturbance after serum treatment fell

into this group. They had been treated vigorously with meningococcal antiserum; three of them proved fatal.

Robinson (1937) also refers to disturbances of the central nervous system after intraspinal injection of serum, characterized either by nuchal rigidity, convulsions, coma, pleocytosis and death, or by bizarre manifestations such as urticaria, aphasia, partial hemiplegia, hemianopsia and papilloedema.

DISCUSSION

These few cases need little discussion. It seems clear that cerebral lesions after the parenteral injection of serum, though far less common than lesions of the peripheral nerves, have the same general aetiology. They come on ten days or so after the injection and are essentially a complication of serum sickness which, as already seen, is a manifestation of allergy.

19

GENERAL ANAPHYLAXIS AFTER ANTISERA

Anaphylactic shock

INCREASED sensitiveness to a second dose of serum has already been noted under serum sickness (p. 141). The graver effects of this hypersensitiveness must now be considered.

It was Richet and his collaborators (Portier and Richet 1902, Richet 1907) who found that the injection of a foreign tissue extract into dogs might lead to increased susceptibility rather than to increased resistance, so that a second dose of the same material evoked a characteristic and rapidly fatal reaction. For this unexpected inversion Richet coined the term *anaphylaxis*.

Already in 1896 Gottstein had collected records of fifteen deaths occurring after the injection of diphtheria antiserum, though, except in one case that proved fatal within five minutes of injection, it was impossible to say how far death was due to the disease and how far to the serum treatment. Further cases continued to be reported. The reason for these fatalities was not understood at the time, but the observations of Richet followed, as they were, by a profound study of the phenomenon of anaphylaxis by Rosenau and Anderson (1906, 1907) in the United States, combined to clarify the problem.

Working with guinea-pigs, Rosenau and Anderson found that a single injection of normal horse serum caused no ill effect, but that, if it was repeated after a minimal interval of ten days, it gave rise within a few minutes to acute respiratory embarrassment, paralysis, convulsions, and death within half an hour. Only a very small quantity of serum was required to sensitize the animal; usually 0.001-0.04 ml sufficed, but in one animal even 0.000 001 ml proved effective. The dose required to evoke shock was likewise quite small—usually 0.1 ml when injected intraperitoneally. When injections of serum were spaced by shorter intervals than ten days, their effect was to immunize rather than to sensitize the animal.

Further experiments showed that guinea-pigs could be sensitized to horse serum by feeding them on raw horse meat; that sensitivity to the toxic action of the serum could be transmitted hereditarily from the mother to her young; and that the hypersensitive state was qualitatively specific in that a guinea-pig sensitized to horse serum reacted only slightly to injection of the serum of other animals. Concentration of diphtheria antitoxin by the Gibson process, which removed much of the globulin, did not destroy the sensitizing power of the serum. Rosenau and Anderson reviewed the literature on the ill effects of serum treatment, and collected records of 19 fatal cases, as well as of many cases that had not been reported in the literature.

The experimental study of the mechanism of anaphylaxis was greatly advanced by Dale (for references see Wilson and Miles 1964*a*) in England who, using a modified Schultz technique, showed that anaphylactic shock resulted from a combination of antigen and antibody in the tissues. It did not occur in an immunized animal because its tissues were protected from

the antigen by the neutralizing effect of the antibody circulating in the blood.

In 1909 Gillette in New York gave a detailed history of 28 cases of collapse or death following the injection of diphtheria antitoxin or, in two cases, of streptococcal antiserum. At this time injections of horse serum—most conveniently available in the form of diphtheria antitoxin—were sometimes given as a treatment for asthma. Nineteen of Gillette's 28 cases were suffering from asthma or bronchial catarrh and were given antiserum; seven received prophylactic or immunizing injections because of diphtheria; and the two remaining patients, one of whom gave a history of hay fever, were injected with streptococcal antiserum in the hope of benefiting their rheumatism. Of the 28 patients, 16 died.

The common history of an acute anaphylactic attack, as illustrated by Gillette's cases, is as follows. Within a few minutes of a subcutaneous injection of antiserum the patient complains of a prickling sensation in the neck and chest, burning of the face and scalp, and itching over the whole body. Breathing becomes laboured and passes rapidly into intense dyspnoea. There is oedematous swelling of the lips, tongue, face, eyelids and neck, and also of the glottis and larynx, followed by cyanosis. Froth may pour from the mouth. Occasionally there is abdominal pain and diarrhoea. The patient is intensely anxious and has a feeling of impending death. Presently respiration stops, unconsciousness supervenes and the patient dies, sometimes within five minutes, sometimes within ten, and sometimes not for half an hour; one of Gillette's cases did not prove fatal for ten hours. Death is due to asphyxia; the heart continues to beat for some time after respiration has ceased. Post-mortem examination may reveal tonic contraction of the bronchioles, dilatation and emphysema of the lungs and distension of the right side of the heart, indicating obstruction to expiration, but the picture is not constant (Bullowa and Jacobi 1930, Vance and Strassmann 1942). In non-fatal cases recovery occurs slowly after a few hours. Urticaria may persist for a day or two.

In most of Gillette's cases anaphylactic shock occurred after the first injection, showing that the patients were already hypersensitive to horse serum. Some of them suffered from horse asthma; some may have been sensitized by eating sausages made up with horse meat; and some may have received a previous injection without knowing of it or without remembering it. Two of the cases, however, had an unusual history in that they did not react till they had been given several doses of antiserum. Case 13, for example, was that of a pregnant woman, with a history of hay fever, who was treated with streptococcal antiserum for subacute polyarticular rheumatism. She received ten units subcutaneously each day for three days, then the same dose at intervals of two or three days. She showed no evidence of serum sensitivity till after the seventh dose on the 15th day of treatment she had an acute anaphylactic attack. She was unable to breathe; the exposed cutaneous surfaces became congested; general oedema appeared affecting the head, arms and legs, accompanied by cyanosis; and the woman's appearance was that of the bloated cadaver of a drowned person. Recovery, however, began after a short time and by the next day she was back to normal. Gillette's case 14 was similar. It was that of an adult man who was given streptococcal antiserum for rheumatism in repeated small doses every three days or so, and who had no reaction till after the tenth dose.

In addition to his 28 cases of immediate collapse or death, Gillette cited one case in which a male asthmatic patient suffering from diphtheria received two doses of serum globulin at an interval of 12 hours. Twenty-

four hours after the last dose he suffered from a severe attack of dyspnoea from which he all but died. Another case was that of a healthy child who was given a prophylactic dose of diphtheria antitoxin. Soon after the injection the boy complained of general weakness and dyspnoea. His health gradually failed over a period of about a year; he lost weight, tired rapidly on exertion, and was unable to play with other children. How far this could be attributed to the serum it is impossible to say.

Little attention seems to have been paid to serum anaphylaxis during the next few years. Waugh (1918) reported a fatal case in a girl suffering from diphtheria; and Weinberg and Séguin (1918) referred to two non-fatal cases in soldiers after intravenous injection of gas gangrene antiserum. Park (1921) in New York, who had a great experience of the treatment of diphtheria by antitoxin, said that about 1 in every 1000 patients suffered a few minutes after injection from nausea, suffocation, and a rapid feeble pulse, but recovered after the administration of appropriate stimulants, with or without artificial respiration; and that about 1 in every 70 000 patients died of anaphylactic shock.

In Germany Pfaundler (1921) found records of three fatal cases of anaphylactic shock among a total of 110 000 patients receiving two injections a week or more apart, but admitted that the real number might be ten times this figure.

In 1924 Lamson in the United States, examining the literature between 1895 and 1923, found records of 41 fatal cases of shock after protein injections; 38 of these had received normal horse serum or antiserum of one sort or another and 3 had had other proteins. Fourteen of the patients gave a history of asthma or hay fever. In twenty-seven death occurred within 15 minutes, in five in 20-35 minutes, and in eight in 45 minutes to 24 hours; in one of the cases the time to death was not stated.

In their paper in 1930 Mackenzie and Hanger added fourteen to Lamson's series of 41 cases, making 55; and noted that death in one asthmatic patient had followed the intravenous injection of as little as 0.06 ml of serum, and in another the subcutaneous injection of 0.5 ml. They drew special attention to the danger of injecting horse asthmatics; it was these patients that had provided most of the deaths. Bullowa and Jacobi (1930) reported a fatal case in a child treated for diphtheria; and reviewed individually a number of previously reported cases. They were struck by the cases that had no history of asthma or of previous injections of serum; and they paid particular attention to the post-mortem findings.

Fatal reactions may follow even the intracutaneous injection of a foreign protein. Freedman (1935) quoted four such cases. In one case of his own a boy who had received an immunizing injection of diphtheria toxin-antitoxin mixture three weeks earlier and had suffered from serum sickness a week later was given an intracutaneous test dose of 0.05 ml of horse serum. Two minutes later a large wheal developed at the site of injection, and urticaria appeared on the face and body. A minute later the child doubled up with abdominal pain. Breathing ceased and intense cyanosis followed. In spite of every attempt to stimulate respiration death occurred in eight minutes.

Vaughan and Pipes (1936) continued the review of the literature undertaken by Lamson (1924) and collected records of 35 cases of anaphylactic shock after the administration of antiserum between 1924 and 1935. Of these, 11 proved fatal, 13 recovered, and the outcome in the other 11 was unknown. In addition, they had reports of 13 more cases given them orally by physicians whom they interrogated personally at a conference they attended.

Rutstein, Reed, Langmuir and Rogers (1941) studied records of reactions to the injection of horse antipneumococcal serum in New York State. They classified those coming on within two hours into (a) thermal, in which fever and a chill occurred immediately after the injection; this type of reaction has already been described under pyrogens (p. 107); (b) anaphylactic, exhibiting the features described on p. 210; (c) circulatory, coming on during or immediately after the injection and characterized by a rapid, thready or irregular pulse, asystole, shock, vascular collapse with sometimes coma, profuse cold perspiration, constricting pain in the chest, a fall in blood pressure and occasionally sudden death; (d) miscellaneous, such as respiratory distress, precordial pain, muscular pain, headache, dizziness or flushing.

In 1938 a total of 2340 cases of pneumonia were treated by intravenous injection of pneumococcal antiserum. Of these, 790 had an immediate serum reaction, of which 218 were thermal, 130 anaphylactic, 67 circulatory, 116 miscellaneous, 244 combined, and 15 doubtful. Thermal reactions occurred in 18.4 per cent of all cases, anaphylactic in 9 per cent and circulatory in 6.2 per cent. During the years 1937-9 about 5500 cases of pneumonia were treated, and 25 deaths definitely attributable to the antiserum were registered; these occurred either from anaphylactic shock or from circulatory collapse, mostly within two hours of the injection.

Kojis (1942), who reviewed the literature, added four more to the fatal cases of anaphylaxis that had been reported, bringing the total up to 77. He personally observed 11 211 patients treated mainly with diphtheria or scarlatinal antiserum; of these, 41 had an anaphylactic attack, i.e. about 1 in 270 patients, and five died (one of these had already been reported by Bullowa and Jacobi 1930). He noted that, though serum sickness was less common after intravenous than after subcutaneous injection, thermal and anaphylactic reactions were much commoner.

Brandl (1943) recorded the case of a boy aged 19 who was given two 1 ml doses of tetanus antiserum at an interval of half a minute. Five minutes later he suffered from laryngeal constriction and itching over the whole body, followed by vomiting, a desire to pass water, and collapse. There was cyanosis of the lips and fingernails, great dyspnoea and pains around the xiphisternum. He recovered under treatment with adrenaline. It was found that he had received a dose of scarlatinal antiserum 12 years previously. It is interesting to note that this boy had an attack of serum sickness five days later.

Vance and Strassmann (1942) reported five fatal anaphylactic cases in children after diphtheria, scarlatinal or tetanus antiserum. Three of the patients died in a few minutes, two not for 6 hours and 14 hours. At autopsy all patients had inflated lungs, the result of bronchial spasm. Post-mortem findings recorded by Gardner (1946) on a boy who died within an hour of receiving tetanus antiserum included innumerable petechial haemorrhages on the mediastinum, the surface of the heart, the costal pleura and the thymus; subpleural haemorrhages over much of the lungs; and distension of the great veins of the neck and the right side of the heart with dark fluid blood. Severe laryngeal oedema was noted *post mortem* by Buff (1960) in a man who died of anaphylactic shock after a skin test dose—0.1 ml of 1/10 dilution—of tetanus antitoxin; and distended emphysematous lungs by Toogood (1960) in a woman who died within ten minutes of a similar, but full-strength, intracutaneous test dose.

To these cases may be added seventeen deaths which were reported to the Ministry of Health between 1935 and 1946, mostly after tetanus or

scarlatinal antiserum, and a further fourteen between 1954 and 1961, all after tetanus antiserum. Since it is estimated that during the latter period about 1 million doses of tetanus antiserum were given annually in England and Wales, the incidence of fatal reactions must be about 1 in 500 000 injections.

Finally reference may be made to a questionnaire issued to about 40 doctors in Barbados, the results of which were recorded by Dr Gale at a meeting in 1965. Altogether 26 cases of acute anaphylaxis had been observed after the injection of antisera, mainly against tetanus, of which three were fatal.

From these findings it seems clear that only a very small proportion of cases and deaths from anaphylaxis can have been recorded in the literature, and that, in view of the extensive use of antiserum in different parts of the world, numerous deaths from anaphylactic shock must occur every year.

PREVENTION OF SERUM ANAPHYLAXIS

Before injecting a patient with serum, it is wise, whenever possible, to inquire into a history of asthma, hay fever, infantile eczema, or other manifestation of an allergic diathesis. Particular care must be exercised in dealing with horse asthmatics and, unless a call for serum treatment is imperative, as in serious cases of diphtheria or tetanus, it is best to refrain from its use altogether. Inquiry must also be made into previous injections of serum. The history of these is often unreliable; and a patient who denies any such experience may naturally be unaware of the fact that a vaccine he has been given, such as diphtheria toxoid antitoxin floccules (TAF) or the older toxin-antitoxin mixture (TAM), contained horse serum. It must be understood, however, that some persons without any allergic manifestations and without any known previous experience of horse serum may react, even fatally, to a dose of antiserum.

To avoid anaphylaxis various methods have been tried, depending partly on testing the sensitivity of the patient and partly on attempting to desensitize him by starting with an extremely small dose and gradually increasing it till the full dose can be tolerated. In practice the intradermal skin test has been widely used for determining the patient's sensitivity. For this purpose 0.1 ml of a 1/10 dilution of normal horse serum is injected *intracutaneously* into one forearm and a similar dose of physiological saline or, better, 1/10 rabbit or sheep serum into the other forearm. Mackenzie (1921) advises waiting for half an hour before deciding whether the reaction is positive or negative. A test is regarded as positive when there is a definite enlargement of the small elevation caused by the injection and the resulting wheal is surrounded by a zone of erythema, provided no similar swelling is visible at the site of the control injection. Some workers lay stress on the size of the wheal and of the surrounding zone of erythema as an index of the degree of sensitivity; thus a wheal that has pseudopodial projections from its circumference is held to indicate a greater degree of hyper-sensitiveness than a small wheal with an entire edge (Mackenzie 1921, Park 1924). Others, however, consider that the rate at which the reaction appears is a better index of the degree of sensitivity than its size (Mishkin 1949).

Other workers still, such as Laurent and Parish (1952, 1958), mistrust the intradermal test altogether. They point out that innocuous substances may give a positive reaction in some persons—though the control test should guard against the risk of being misled by a pseudo-reaction—and, of far greater importance, that acute anaphylaxis may occur in spite of a

completely negative skin reaction. Their experience included over 50 cases of patients who had withstood the intramuscular injection of a full dose of antiserum a few hours after a strongly positive reaction to the intradermal injection of a 1/10 dilution of serum. This led them to conclude that there was no parallelism between skin sensitivity and general sensitivity. Laurent and Parish regard the *subcutaneous* test as much more reliable. They inject 0.2 ml of diluted or undiluted serum beneath the skin and keep the patient under observation for half an hour. If no reaction occurs, they inject the full dose intramuscularly. In an allergic patient or in one with a history of previous serum treatment, they make a subcutaneous test with a 1/10 dilution of serum, and after 30 minutes give 0.2 ml of undiluted serum subcutaneously. If there is no reaction, they inject the full dose of serum, subcutaneously or intramuscularly, after another 30 minutes. They warn against the injection of serum intravenously unless a preliminary intramuscular dose has been well tolerated.

No preliminary test can give complete assurance of safety. Indeed fatal anaphylactic shock may follow the injection of the very small amount of serum used for the skin test. Buff (1960), for example, recorded the case of a man who was injected with 0.1 ml of a 1/10 dilution of tetanus antitoxin. In 20 minutes there was a local wheal with red streaks extending up the forearm, and the patient complained of nausea, general pruritus, and then of dizziness and weakness. His eyelids began to swell; his face became flushed; the pulse was thready and irregular; he became increasingly cyanotic and oedematous; and he died within an hour. Buff found records in the literature of six cases of death after the intracutaneous injection of various antigens, one of which was undiluted horse serum. Freedman (1935) quotes one case in which a boy died eight minutes after an intracutaneous injection of 0.05 ml of horse serum (see p. 213).

An attempt at desensitization may be made by giving increasing doses of serum subcutaneously every half-hour before injecting the full dose intravenously. Mackenzie (1921) cites one case of a man with a positive skin test result who was given seven subcutaneous injections starting with 0.025 ml of serum and going up to 1.0 ml. He was then given a further series of eight intravenous injections, starting with 0.1 ml and finishing with 16 ml; only minor reactions occurred during the process. Martin (1919) advocated the intravenous route of injection with serum diluted ten times with saline; provided the injection was made slowly, he regarded this method as free from danger. Here again, experience teaches the fallacy of over-confidence. Park (1928), for instance, records the case of a young woman who was given four subcutaneous desensitizing injections of serum—0.5, 1, 2 and 4 ml—without any appreciable reaction. She was then injected very slowly with serum by the intravenous route. After 10 ml had been given, she complained of premonitory symptoms of shock. The injection was stopped, but without avail. The symptoms increased and death followed shortly fterwards.

It is clear that no method of preliminary testing or of desensitization can be relied upon completely to prevent anaphylactic shock. The possibility of such an accident must be guarded against as far as possible, but so long as serum treatment is used, so long must the risk of this alarming complication be faced.

Incidentally it is said by Wolfsohn (1944) that anaphylactic shock does not occur in the presence of general or local anaesthesia. He therefore advocates infiltration of the skin with a 1 per cent solution of novocaine and the usual amount of adrenaline around the site into which the serum is

to be injected unless an operation is to be performed under a general anaesthetic.

It is hardly necessary to add that whenever an injection of serum is given adrenaline or epinephrine should always be at hand for use at the first sign of anaphylactic shock. Valuable, however, as these drugs are, they are not always able, even in repeated dosage, to prevent death.

20

GENERAL ANAPHYLAXIS AFTER VACCINES

Anaphylactic shock

THOUGH THE occurrence of acute and often fatal anaphylactic shock after the injection of antiserum is well documented, reports on acute allergic manifestations after the administration of vaccines of various kinds are scanty and the number of fatal accidents on record is small.

Lintz (1917) appears to have been one of the first to describe a severe post-vaccinal attack. A senior student who was given the first dose of the US Army typhoid vaccine experienced an acute reaction coming on in 20 minutes, characterized by chilliness and headache, followed by continued vomiting of mucus and blood, extreme soreness over the whole body, pain in the joints, a temperature of 103°F, and at the height of the reaction severe collapse. The fever, vomiting, soreness and painful joints lasted for 48 hours, but during the following days there were anorexia, haematuria, and enlargement of the lymphatic glands in the neck, axilla and groin. The patient recovered in about a week. There was very little local reaction and there was no history of previous sensitization or of allergy in any form.

In their review of the literature from 1923 to 1935 Vaughan and Pipes (1936) include two cases of acute anaphylaxis after vaccines—one after a common-cold vaccine and one after the intracutaneous injection of a streptococcal vaccine. Ziskind and Schottenberg (1938) describe one of the few fatal cases. An arthritic woman who was being treated by protein therapy was injected with 0.06 ml of typhoid vaccine intravenously and five days later with 0.15 ml. Thirty minutes after the second injection she collapsed and died almost immediately. Post-mortem examination revealed congestion of the liver and other viscera with dilatation of the hepatic sinusoids and alveolar capillaries of the lungs.

In his review of 61 042 persons injected with tetanus toxoid in the Royal Air Force Whittingham (1940) found only two cases of acute anaphylaxis. The first was in a man of 52 years who was given a reinforcing injection. Within 15 minutes his lips swelled, he had vomiting and diarrhoea, and lost consciousness; by next day he had recovered. The second was in a man of 24 years who, ten minutes after his second injection of toxoid, experienced dizziness, flushing, swelling of the lips, gums and cheeks; he rapidly became dyspnoeic and vomited twice. An urticarial rash came out over his whole body and lasted for eight hours. This man likewise recovered. Both patients were found by a skin test to be highly sensitive to Witte peptone, the first to a 1/10 000 and the second to a 1/1000 dilution.

Similar suspicion of Witte's peptone used in preparing tetanus toxoid was expressed by Parish and Oakley (1940) in the case of a woman who had a reaction within 10 minutes of a second injection. Symptoms included flushing of the face and hands, acute abdominal pain, cold clammy sweating, incoherent speech, and later itching of the scalp and in between the toes with some urticaria and a scarlatiniform rash. After intracutaneous injection of a 1/1000 dilution of Witte peptone she had itching of the nose and tongue, slight swelling of the lower lip, smarting of the eyes and flushing of the face.

Both Parish (1936) and Bousfield (1936) recorded cases of acute reactions after schick tests. Parish traced seven cases in the literature and had notes of seven other cases. Usually symptoms came on in a few minutes and consisted of swelling and wheal formation at the site of injection, puffiness of the face, generally an urticarial or occasionally a scarlatiniform or erythematous rash, faintness, cyanosis and dyspnoea. All patients were well by the following day. Parish suspected the Witte peptone used in preparing the schick reagent. So also did Bousfield, who recorded two similar cases; in one of these the child reacted to a scratch test with a 1/10 000 dilution of Witte's peptone.

In the United States Cooke, Hampton, Sherman and Stull (1940) had experience of four patients who were sensitive to tetanus toxoid, and to either the Witte or Berna peptone with which it was prepared. Long (1943), describing the practice of routine immunization with tetanus toxoid in the United States Army, said that about 0.05 per cent of injections, i.e. 1 in 2000, was followed by an acute allergic reaction—flushing and itching of the skin, local and general urticarial eruptions, oedema of the lips and eyelids, and occasionally oedema of the glottis with dyspnoea. The reacting patients were found to be sensitive to the intracutaneous injection of 0.1 ml of a 1/100 dilution of the toxoid, and to the Witte or Berna peptone it contained. When toxoid was prepared without either of these peptones, the incidence of severe reactions fell to about 1 in 10 000 injections.

Allergy to egg protein is held to be responsible for some cases of post-vaccinal shock. Ratner and Untracht (1946) say that about 1 per cent of the American population is allergic to chick egg proteins. They reported that 11 out of 108 allergic children reacted to a test dose of 0.02 ml of influenza vaccine made from chick embryo. Each of these children was found to be sensitive to egg-white protein. Curphey (1947) ascribed a fatal case of anaphylaxis after influenza vaccine to the same cause. A child of three years suffered from abdominal pain, chills, vomiting and convulsions four hours after an injection of 0.5 ml of a stock influenza vaccine made from chick embryo. The rectal temperature went up to 109°F and the pulse rate to 240 a minute. There were severe shock and collapse followed by death within 7-8 hours. At post-mortem blood was found in the nose and vagina and haemorrhages in the thymus, epicardium and lungs.

Werne and Garrow (1946) described two fatal cases in identical twins 16 and 20 hours after a second injection of diphtheria-pertussis vaccine. Soon after the injection they both cried, vomited, consumed excessive amounts of water, and became unconscious; both were dead by the following morning. At post-mortem widespread lesions were found referable to arterial spasm and increased endothelial permeability. Death was ascribed to delayed anaphylactic shock, but it is perhaps more probable that these cases belonged to that group of unexplained reactions which occur after pertussis vaccine (see p. 195).

Between 1938 and 1946 ten cases of acute anaphylaxis, seven of which were fatal, were reported to the Ministry of Health. Two were after alum-precipitated diphtheria toxoid (APT), three after tetanus toxoid (TT), two after typhoid-paratyphoid vaccine (TAB), and two after combined TAB and TT. The three non-fatal reactions were all after tetanus toxoid.

An unusual case of acute anaphylaxis occurred after the intracutaneous injection of 0.1 ml of BGG vaccine. The patient, who had a history of bronchial asthma, collapsed a few minutes after the injection, was pulseless for a short time, but recovered under treatment (Vollset 1965).

Sanarelli-Shwartzman phenomenon

Finally may be mentioned two fatal cases after therapeutic injections of typhoid-paratyphoid vaccine which appear to be examples of the Sanarelli-Shwartzman phenomenon. Experimentally, when a rabbit is injected intradermally with a filtrate of a typhoid culture and 24 hours later is given another dose intravenously, a haemorrhagic necrotic lesion appears within a few hours at the site of the intracutaneous injection (see Shwartzman 1937). When both doses are given intravenously, a general haemorrhagic reaction follows characterized by naked-eye cutaneous and visceral haemorrhages, and histologically extravasations of blood in the veins of the liver, spleen, pancreas and lungs, and arterial necrosis in the cortex of the kidneys, the adrenals and the bone marrow (Sanarelli 1924). The reaction does not occur unless at least eight hours are allowed to elapse for the preparatory dose to sensitize the tissues and unless the provoking dose rapidly floods the tissues with the antigen, as by the intravenous route.

A case exemplifying the general reaction was reported by Urbach, Goldburgh and Gottlieb (1944) in a woman aged 40 years, who was injected with TAB vaccine in an attempt to cure a persistent pain in the back. Two to three hours after the third daily injection, which was made intravenously, her temperature fell precipitously, her pulse went up to 140 a minute, her blood pressure dropped to 50/20, and in 6½ hours she died. At post-mortem the lungs were found to be very congested and oedematous; petechiae were present in the endocardium and parietal pericardium and on the surface of the liver; and there were linear haemorrhages in the kidney. Microscopically necrotic lesions were seen in the kidney, adrenal and liver.

A second case, described by Love and Driscoll (1945), was in a man suffering from choroiditis. He was given two intravenous injections of TAB vaccine, each of 0.1 ml, on two successive days. Within 1½ hours of the second dose his temperature rose to 107°F and his pulse rate to 160. Next morning the respirations were up to 48 a minute. The following day he had nausea, vomited old blood, and started to hiccough. Later he became restless and confused. He died suddenly three days after the second dose. At post-mortem generalized petechiae were found throughout the parenchymal organs and brain, and there was massive necrosis of the liver and kidney.

PREVENTIVE MEASURES

In practice there is little that can be done to protect against the acute allergic reaction after vaccines. When possible, the subject to be vaccinated may be questioned on a history of allergy and a preliminary small intracutaneous injection made to test for sensitivity; but when mass vaccination has to be carried out, precautionary measures of this sort are impracticable. An exception should be made for vaccines such as influenzal, rickettsial, or yellow fever vaccines that are prepared in chick embryos; when these are to be given, it is well to inquire about sensitivity to egg proteins. To patients with a history of allergy to penicillin or eggs or with a history of eczema Kawchak (1966) recommends the administration of a tablet of an antihistamine, such as chlorpheniramine, some minutes before the injection of the vaccine. In his experience this prevents any untoward reactions. Witte and Berna peptones should not be used in media in which bacteria for vaccines are grown.

Multiple vaccines on the same day should not be given. The example of the hardy colonel who insisted on being vaccinated against smallpox, typhoid fever, diphtheria and tetanus all on the same day and died the same night is not one to emulate.

The Sanarelli-Shwartzman phenomenon should be borne in mind, and intravenous injections on two successive days even with different vaccines—for the phenomenon is not specific—should be avoided.

21

ABNORMAL SENSITIVITY OF PATIENT: SKIN COMPLICATIONS OF SMALLPOX VACCINATION

SMALLPOX VACCINE has probably been followed by more complications and been responsible for more deaths than any other vaccine. The complications may be classified into two main groups, those affecting the skin and eyes and those affecting the central nervous system. The latter group has already been dealt with in Chapter 15. In the present chapter the skin and eye complications will be described. For a general review of vaccination against smallpox see Lentz and Gins (1927), and for a detailed review of the complications of smallpox vaccination see Czerny and Opitz (1927) and Herrlich, Ehrengut and Schleussing (1965*c*).

The skin and eye complications of vaccination

Jochmann (1913) recognizes the following forms:

(a) *Polymorphic vaccinial exanthems.* These usually occur 7 to 14 days after vaccination. The rash, which is roseolar, morbilliform or urticarial, appears first on the face and soon after on the trunk and extremities. Spots may be as large as 12 mm in diameter and may become confluent.

(b) *Generalized vaccinia.* This appears usually on the 9th or 10th day and is due to haematogenous spread of the virus. It is characterized by small pustules that heal without scarring. The oral mucosa as well as the skin may be affected. Occasionally generalized vaccinia has been seen in persons who have swallowed the vaccine, usually after an incubation period of six days.

(c) *Autogenous vaccinia.* Auto-inoculation of any part of the body may occur but is particularly common in the eyes and on the genital organs—scrotum and vulva—with spread to the inner aspects of the thighs. The ocular disease is generally unilateral and affects the palpebral and less often the bulbar conjunctiva; it may spread to the cornea, and sometimes leads to keratitis, iritis, panophthalmitis and loss of the eyeball. Susceptibility to auto-inoculation ceases on the 12th day after vaccination.

(d) *Eczema vaccinatum.* This becomes visible on the third or fourth day. An existing dry eczema passes over into the wet form, and this is succeeded by redness and swelling increasing in intensity. The surface takes on a dark red haemorrhagic appearance, is nodular, and is covered with a partly purulent discharge. Around the edge of the area affected are numerous pustules that gradually coalesce centripetally and convert the area into a swollen mass having a bacon-like background with an abundant yellowish and extremely offensive secretion over it. The regional lymphatic glands are swollen and there is high fever, accompanied in fatal cases by generalized infection, delirium, unconsciousness and death. The vaccinial eruption is said not to spread beyond the eczematous area, and, in spite of its severity, to heal with little or no scarring. Incidentally

patients who have recovered from such an attack may find that their eczema is cured.

Jochmann does not mention vaccinia gangrenosa, or chronic progressive vaccinia as it is sometimes called, but he does say that wounds may be infected with vaccinia and occasionally become gangrenous; and that at one time erysipelas used to be common after vaccination.

It is manifestly impossible in such a short volume as this to review the skin complications of vaccination in their completeness, even if they were all known. Many of the minor cases are probably never seen by a general practitioner, and many cases seen by general practitioners are probably never reported. Classification of skin lesions is subject to differences of opinion among dermatologists, and the exact relation of some lesions to vaccination is often in doubt.

In view of the lack of uniformity in both the quality and quantity of the information available, it seems wise to consider individual collections of figures and appreciate the degree of variation between them, before attempting to estimate the probable average incidence of the different complications.

ENGLAND AND WALES: GENERALIZED VACCINIA

Early figures

An investigation at the Ministry of Health of records sent in by public vaccinators showed that, during the four years 1909-10 and 1921-2, taken at random, and the ten years 1932-41, 35 cases of generalized vaccinia were noted among a total of 3 289 733 vaccinations, i.e. an incidence of 1 in 94 000. There were four deaths—a case-fatality rate of 11.4 per cent and a mortality of 1.1 per million vaccinations (Jubb 1943).

It was noted that non-vaccinial rashes associated with vaccination were not uncommon, occurring once in about 8000 vaccinations. Whether these non-specific rashes are caused by circulation in the blood stream of the 'secondary products of inflammation absorbed from the vaccine-pustule' (Ricketts and Byles 1908), or are due to some other cause, is not clear. After primary vaccination they are most common between the 7 th and 13th days.

Chalke (1931) stated that in a London Metropolitan Borough he had seen 14 cases of a generalized rash—by which he means a non-specific rash—among 1600 persons vaccinated, i.e. 1/114. This is an unusually high incidence.

1951-60 figures

From 1951 onwards records were received by the Ministry of Health from local authorities, including general practitioners, of the occurrence of generalized vaccinia, post-vaccinal encephalomyelitis, or death from other complications in recently vaccinated persons.

During the ten years 1951 to 1960 about five million official vaccinations or revaccinations were carried out among the civilian population. Generalized vaccinia was reported in 186 cases (Conybeare 1964).

The term *generalized vaccinia* was applied to cases in which an eruption occurred elsewhere than at the vaccination site, which seldom appeared before the sixth day after vaccination, and which passed through a vesicular stage. From this category auto-inoculation was excluded, as was also heterogenous vaccinia, and no figures were provided for either of

these complications. The cases of generalized vaccinia were subdivided into three clinical groups:

(a) **Chronic progressive vaccinia.** This is defined as a severe and progressive illness in which the lesion at the site of a successful vaccination, although initially normal, fails to heal, and then becomes necrotic, steadily increasing in size until it may cover a large area of skin. Similar lesions soon appear elsewhere on the body, and continue to do so, following the same course, till after a period of many weeks or months death occurs either from overwhelming toxaemia, from viraemia, or from septicaemia due to secondary bacterial infection. Such cases are sometimes referred to as *vaccinia gangrenosa.* Eight of the 186 cases of generalized vaccinia were of this nature. All were in primarily vaccinated infants of six months or less; seven of them proved fatal.

(b) **Eczema vaccinatum.** This form occurs in persons suffering from or having a history of eczema, or, according to McKhann and Ross (1938), some other skin disease such as impetigo, intertrigo or secondary syphilis. Either coincident with or soon after the development of the local lesion at the site of vaccination a vaccinial eruption occurs, usually on one or more parts of the body that are at the time eczematous or that have previously been so. These areas become intensely inflamed and, later, the eruption may spread to healthy skin. The associated illness is severe; the temperature rises, there may be general enlargement of the lymphatic glands, and in infants as soon as large areas of skin have become affected the prognosis is grave. Eczema vaccinatum or eczema vaccinformis seems to be indistinguishable from Kaposi's varicelliform eruption, which, according to Fries, Borne and Barnes (1948), is itself indistinguishable from eczema herpetiformis. Sixteen cases of eczema vaccinatum, of which four were fatal, were reported in this series. The four fatal cases were all in infants under one year who died 4-16 days after the onset.

(c) **Benign generalized vaccinia.** This term includes cases in which, although the local lesion at the site of vaccination matures in the manner expected of a primary 'take', there also appear at about the same time—9 to 14 days as a rule—on other areas of healthy skin papular lesions that become vesicular and resemble those of primary vaccinia in their subsequent development, except that, when profuse, they may vary greatly in size (Jubb 1943). The accompanying constitutional disturbance is comparatively mild and gives rise to no anxiety. Under this heading 162 cases were grouped, of which 150 were associated with primary vaccination. Of the 162 cases, 106 were in infants under one year of age.

1962 Figures

As a consequence of outbreaks of smallpox in England and Wales during the early part of 1962 a total of about three and a quarter million persons received primary vaccination. Copeman and Wallace (1964), who obtained access to records from three different sources, were able to collect a total of 185 cases of eczema vaccinatum—an incidence of 1 in 18 000. All, with one exception, followed primary vaccination. Of the 185 cases, detailed information on 137 showed that 87 were males and 50 females; 67 were under five years of age; and 89 had contracted vaccinia accidentally, as a rule from some vaccinated member of the family. Eleven of the 185 cases proved fatal—a fatality rate of 6.7 per cent. Two-thirds of the 123 cases reported on by dermatologists did not have active eczema at the time of vaccination. Of the 185 cases, 35 were in Wales, and are

included in the series that follows described by Waddington and his colleagues (1964).

SOUTH WALES : VACCINIAL AND NON-SPECIFIC ERUPTIONS

During an outbreak of smallpox in South Wales in 1962 about 900 000 persons were vaccinated. One of the smallpox consultants had an almost unique opportunity of observing the cutaneous complications of vaccination. Though not every case can have been referred to him, it is probable that he saw all the more severe eruptions. The figures, which were reported by Waddington, Bray, Evans and Richards (1964), included 35 cases in the series just described of Copeman and Wallace (1964).

(a) *Local complications.* Necrosis and ulceration 48; keloids not preceded by ulceration 21; others 8. *Total* 77.

(b) *Eruptions, non-vaccinial, occurring at a distance from the vaccination site, i.e. non-specific reactions*

Erythema multiforme	41	Urticaria	10
Toxic erythema	21	Others	5
Anaphylactoid purpura	15	*Total*	92

(c) *Eruptions composed of vaccinial vesicles*

Autogenous vaccinia	21	Chronic progressive vaccinia	2
Eczema vaccinatum	35	Foetal vaccinia	2
Heterogenous vaccinia	5	*Total*	73
Benign generalized vaccinia	8		

Of the 48 cases of local necrosis and ulceration, only three were in children. The adults had a severe reaction with erythema and induration of the upper arm lasting for 2-3 weeks, followed by the development of a thick crust which adhered to the skin for as long as 10 weeks. Removal of the crust disclosed a deep punched-out infected ulcer, which took 6-8 weeks to heal; in 14 of the cases a keloid formed in the scar.

The incidence of non-specific eruptions was about 1/10 000. Of the 92 patients affected, 89 were regarded as suffering from a vascular reaction, and three from a dermatosis provoked by vaccination—psoriasis and lichen planus.

In the 21 cases of autogenous vaccinia the lesions appeared 6-9 days after vaccination, and affected mostly the eyelids, vulva and perineum.

Thirty-five patients who had atopic eczema or a history of it suffered from a generalized vaccinial eruption, and two of them died. Over 50 per cent of the cases were in children under five years of age; males were nearly twice as commonly affected as females; and in 74 per cent of all cases infection had occurred accidentally through contact with recently vaccinated parents or siblings. The onset was usually sudden; the lesion matured rapidly to form deep umbilicated pustules resembling those of variola; there was usually an abrupt transition between a confluent and a sparse rash on adjacent areas; and the regional lymph nodes were greatly enlarged.

The eight cases of benign generalized vaccinia were all mild. In this disease it is stated that the patient has a normal skin, the eruption occurs between 4 and 14 days after vaccination, fever is of short duration, the distribution of the rash is indiscriminate, the lesions are usually smaller and more superficial than those of smallpox and maturation is rapid. The incidence in this series was rather less than 1/100 000.

The two patients who suffered from chronic progressive vaccinia—vaccinia gangrenosa—both recovered. Both of them were leucaemic and both were treated by blood transfusion.

In the two cases of foetal vaccinia primary vaccination of the mother had been carried out at 19 weeks and 6 months of pregnancy respectively. The foetus of the first mother was stillborn in a macerated condition at 23 weeks, but the foetus of the mother vaccinated at 6 months, though born prematurely at 32 weeks, with widespread lesions on the face, trunk and limbs, survived.

In none of the British reports does any mention seem to be made of the 'raspberry excrescence' or 'raspberry sore' referred to by Fox (1902). The lesion usually appears 3-7 days after vaccination, looking like an ordinary vaccinial papule but, instead of going on to vesiculation and pustulation, it remains as a hard, dense, bright red nodule resembling a naevus; it may persist for weeks or months.

EDINBURGH 1942: VACCINIAL ERUPTIONS

After being free from smallpox for 22 years, Edinburgh suffered a small outbreak in the late autumn of 1942.

Infection was introduced into the Royal Infirmary in a manner that was never satisfactorily determined, though it was almost certainly by indirect spread from Glasgow. There were 36 cases, of which 8 proved fatal. Mass vaccination was carried out partly at the time of the Glasgow outbreak in June and July, and partly at the time of the outbreak in Edinburgh itself in October and November (Report 1944). A total of 274 000 persons were vaccinated, of whom roughly three-quarters had been previously vaccinated successfully. About two-thirds of all those vaccinated were over 15 years of age. The method of vaccination consisted mainly of three parallel scratches three-quarters of an inch long and a quarter of an inch apart for revaccinations and of one scratch only for primary vaccinations. The complications that were observed and reported were as follows:

A. Non-specific eruptions on parts of the body distant from the vaccination site, mainly of the erythema multiforme type. 34, or 1/8000 vaccinations.
B. Severe local reactions. No figures given for the whole vaccinated population owing to the difficulty of deciding what constituted a severe reaction, but in one institution 2 per cent and in another 6 per cent of severe reactions were recorded.
C. Autogenous vaccinia, due to auto-inoculation. 14.
D. Heterogenous vaccinia, i.e. infection of an unvaccinated person. 6.
E. Benign generalized vaccinia. 3, or 1/90 000 vaccinations.

No cases of eczema vaccinatum, progressive vaccinia or foetal vaccinia were recorded, and no deaths occurred as the result of vaccination.

It may be noted that, in the Glasgow outbreak earlier in the same year, 123 non-specific rashes were reported among about 500 000 persons vaccinated, i.e. 1/4000 (Bloch 1942).

UNITED STATES OF AMERICA: VACCINIAL ERUPTIONS

New York City, 1947

In March and April 1947 twelve cases of smallpox occurred in New York City. Mass vaccination was resorted to, and the number of persons vaccinated was about six million. Greenberg (1948), who tried to collect as many cases as possible of vaccinial complications, reported on 45 cases of a generalized vaccinial eruption. Of these, 38 had a history of pre-existing eczema and may be classified as eczema vaccinatum. The remaining seven cases were apparently cases of benign generalized vaccinia. Of the 38 patients that suffered from eczema vaccinatum, 35 were under five years of age, and 28 had not been vaccinated but had picked up the infection from a vaccinated contact. Two of the cases, both in unvaccinated infants, proved fatal.

Fries, Borne and Barnes (1948), who reported on the same outbreak, paid special attention to the occurrence of eczema vaccinatum, or, as they prefer to call it, Kaposi's varicelliform eruption after vaccination. They collected 43 cases of this complication, of which 4 per cent—presumably two patients—were fatal. They investigated 16 of these cases personally, and found that all of them had atopic eczema; 10 of them were allergic to special foods. The rash was accompanied by high fever, intense pruritus, restlessness and facial oedema coming on 5-19 days after the date of probable exposure to a vaccinated contact. There was great enlargement of the regional lymph nodes, which sometimes actually fluctuated. The fever lasted 5-7 days and came down by lysis. The eruption was confined almost entirely to the eczematous areas, and the vesicles and pustules were often umbilicated. All the patients were under seven years of age, 13 of the 16 were males, and none of them had been vaccinated. Fifteen of them were vaccinated four weeks after admission and all gave an immune reaction.

Curth, Curth and Garb (1948) also reported on the New York outbreak. Their observations were confined to cases seen privately and in clinics. Among them were two cases of auto-inoculation, affecting the mouth and the female genital organs, and six cases of generalized vaccinia—all mild—and numerous cases with non-specific eruptions, mainly erythema multi-forme.

Later figures

Three sets of figures are available for recent years. Some of these probably overlap, but it is impossible to say to what extent.

In 1960 Kempe reported on 256 cases. Unfortunately, his communication, which is concerned primarily with treatment by vaccinial globulin, does not say where or when these cases occurred, but the presumption is that they were in the United States between the years 1955 or thereabouts and 1960. They comprised 62 cases of generalized vaccinia, 132 of eczema vaccinatum, 23 of vaccinia necrosum, 27 of auto-inoculation, and 12 of encephalitis (see p. 171). Incidentally Kempe said that only nine cases of vaccinia necrosum had been reported in the literature; this was clearly an understatement. He himself added 23 further cases.

Five years later Neff (1965) reported on an immunization survey made in 1963. In that year 6 200 000 primary vaccinations were carried out in the United States. Among these there were 560 complications of which 432 were followed up. They included 329 in those primarily vaccinated, 17 in those revaccinated, and 86 in unvaccinated contacts. Besides 11 cases of encephalitis (see p. 165), there were 134 of

generalized vaccinia, in of eczema vaccinatum, 9 of vaccinia necrosum, 115 of auto-inoculation, and 52 others.

Sussman and Grossman (1965) said that, as west coast consultants, they saw 336 patients suffering from complications of vaccination between July 1960 and the end of 1963. There were 143 cases of generalized vaccinia, 58 of eczema vaccinatum, 6 of vaccinia necrosum, 82 of auto-inoculation and accidental infection, 5 of encephalitis and 42 others. Some of these cases were probably included in Neff's (1965) series.

Though the figures given by Kempe (1960) and Sussman and Grossman (1965) show that skin complications of vaccination are fairly common, they do not enable an estimate to be made of their incidence, because the number of persons vaccinated among whom they occurred was not known. On the other hand nearly all of the complications listed by Neff (1965) occurred among 6 200 000 persons vaccinated for the first time, and their incidence is therefore given in Table 9 (p. 236).

GERMANY! VACCINIAL ERUPTIONS ON SKIN AND EYES

Though far from complete, a well-documented account of the complications of smallpox vaccination in the German Federal Republic during the years 1946-57 is given in a report (1959*a*) of the German Ministry of Health. So far as the skin and eye complications are concerned, they may be listed as follows:

Skin		
(a)	*Severe inflammatory reactions,* including 7 cases of erysipelas and 6 cases of septicaemia or pyaemia	33
(b)	*Post-vaccinal exanthem, non-specific*	11
(c)	*Eruptions composed of vaccinial vesicles*	
	Autogenous vaccinia (vaccina secundaria)	31
	Eczema vaccinatum	6
	Heterogenous vaccinia (vaccina inoculata)	27
	Benign generalized vaccinia (vaccina generalisata)	22
	Keloid of scar	6
Eye		
Vaccinia of the lids or cornea		16
Other affections		3
		155

Unfortunately the number of vaccinations performed during this period is not given. Figures for first vaccinations, however, for the years 1950-6 are available for the Federal Republic, except for Hamburg and North Rhine Westphalia, which apparently failed to provide information on either the number of vaccinations carried out or on the complications observed. If these two areas are omitted, and it is assumed that the number of vaccinations during the years 1946-9 and during 1957 were of the same annual order as that during 1950—6, it may be calculated that the total number of primary vaccinations during the twelve years 1946-57 was about 6 220 000. The incidence of some of the skin complications can then be estimated as follows:

Severe inflammatory reactions	1/190 000
Non-specific post-vaccinal exanthem	1/570 000
Autogenous vaccinia, including eyes	1/125 000
Eczema vaccinatum	1/1 000 000
Heterogenous vaccinia	1/230 000
Benign generalized vaccinia	1/280 000

Rather more exact figures are given by Herrlich (1954) for Bavaria. During the years 1945-53 there were reported three cases of eczema vaccinatum and twelve of generalized vaccinia among a total of about 1 150 000 primary vaccinations. This gives an incidence of 1/380 000 for eczema vaccinatum and of 1/96 000 for generalized vaccinia. Both these figures are considerably higher than for the Federal Republic, suggesting that reporting or the collection of reports from other Lander was less complete than in Bavaria.

DISCUSSION ON SKIN LESIONS

At the beginning of this section reasons were advanced to explain why all our figures on the skin complications of vaccinia are incomplete. Several additional reasons might be advanced, but they would serve little useful purpose. It is sufficiently clear that the comparison of rates in different countries, or from time to time in the same country, is not really justifiable. Nevertheless the figures have been collected and reproduced as rates per million vaccinations in Table 9.

TABLE 9. Skin complications of vaccination: rates per million vaccinations

Place and time	Necrotic local lesions	Non-vaccinial eruption	Heterogenous vaccinia	Autogenous vaccinia	Eczema vaccinatum	Benign generalized vaccinia	Chronic progressive vaccinia
London Metropolitan Borough 1931	—	8800	—	—	—	—	—
England and Wales up to 1941	—	129	—	—	—	10·6	—
England and Wales 1951–60	—	—	—	—	3·2	32·4	1·6
England and Wales 1962	—	—	—	—	185	—	—
S. Wales 1962	85·6	102	5·6	23·3	38·9	8·9	2·2
Edinburgh 1942	—	124	21·9	51·1	0	10·9	0
New York 1947	—	—	—	—	6·3	1·2	—
Germany[1]— Federal Republic 1946–57	5·3	1·8	4·3	8·0[3]	1·0	3·5	—
Bavaria[2] 1945–53	—	—	—	—	2·9	11·4	—
USA[4] 1963	—	—	14	19	18	22	1·5

[1] Omitting Hamburg and North Rhine Westphalia; primary vaccinations.
[2] Primary vaccinations.
[3] Includes eye lesions, which occurred at a rate of 3·1 per million.
[4] Mainly primary vaccinations.
— Means no information.

A glance at these figures indicates something of the enormous reporter or observer error that must exist. It is impossible to believe, for example, that there were, in Germany, only 1.8 cases per million showing a non-specific rash when in a London borough there were 8800 cases per million. In the London borough the 1600 vaccinated children were under

fairly close observation (Chalke 1931), so that probably few general rashes were missed; whereas in Germany the reporting of such rashes must have been very poor indeed. Several years previously, however, Jochmann (1913) mentioned the occurrence of rashes affecting 12 out of 100 children vaccinated.

The figures for England and Wales, South Wales, and Edinburgh are in quite good agreement with each other in so far as non-specific rashes are concerned, but differ considerably for the incidence of eczema vaccinatum and benign generalized vaccinia. One reason for this is probably the difference in practice of deciding whether or not to ascribe a case of generalized vaccinia to eczema or not. In New York, for instance, Greenberg (1948) assigned no fewer than 38 out of 45 cases of generalized vaccinia to the category of eczema vaccinatum; and much the same tendency was apparently operative in South Wales where all the cases were seen by one observer (Waddington *et al.* 1964).

Other workers would ascribe practically all cases of generalized vaccinia to auto-inoculation (Chalke 1931), but many would dispute this as being very improbable. Herrlich, Ehrengut and Schleussing (1965*c*) maintain that generalized vaccinia is the result of a viraemia and affects perfectly healthy skin. Two things that seem clear are that eczema vaccinatum is a complication restricted almost entirely to young children, principally males, and that it frequently occurs at a time when there is no visible eczematous rash.

Chronic progressive vaccinia, or vaccinia gangrenosa, appears from the few available figures to occur very seldom.

DISCUSSION ON THE EYE LESIONS

Vaccinia of the eyelids, conjunctiva and cornea is mentioned only in the German statistics, where the rate was 3.1 per million. Experience, however, of the five outbreaks of smallpox in England and Wales in 1962 showed that ocular lesions, apparently resulting from auto-inoculation, were by no means uncommon.

The French, moreover, have devoted some attention to this subject. For example, in the outbreak of smallpox at Marseille in 1952 about 850 000 vaccinations were carried out. Sédan, Ourgaud and Guillot (1953) record that, among these, 19 cases of ocular complications were noted. Nine affected the palpebral conjunctiva, six the cornea, one the iris and three the oculomotor system. In these last three cases, besides paralysis of the extrinsic eye muscles, other parts of the body were affected. One had the Guillain-Barré syndrome, another a meningo-encephalitis, and the third an encephalitic reaction starting on the day of vaccination and characterized by headache, fever and diplopia. Ocular complications are said to be as common after revaccination as after primary vaccination; the cornea does not appear to become immunized so that second attacks may occur. Revaccination, too, may reactivate the original disease, as happened in a patient observed by Sédan (1965), who suffered again from diplopia and from general disturbance of the nervous system when she was revaccinated seven years after her primary attack.

Other occasional complications of vaccination, such as pharyngeal angina, myocarditis, pneumonia, nephritis and osteomyelitis, occur too seldom for any reliable figures of incidence to be given (see Herrlich *et al.* 1965*c*).

When human lymph used to be employed for vaccination syphilis, tuberculosis and leprosy were all occasionally transferred (Jochmann 1913).

Kotlarek-Haus, Wojewódzka and Lech (1965) describe three cases of chronic lymphocytic leucaemia coming on some weeks after smallpox vaccination, but how far vaccination was responsible it is impossible to say.

SECONDARY BACTERIAL CONTAMINATION OF THE VACCINIAL LESION

Apart from post-vaccinal tetanus, which is dealt with separately (p. 99), secondary contamination with various organisms may occur at the site of inoculation with smallpox vaccine. At one time post-vaccinal erysipelas, due presumably to infection with *Streptococcus pyogenes,* was not uncommon, as were also impetigo contagiosa and suppurative regional lymphadenitis. Occasionally diphtheritic infection occurred resulting in the formation of a dirty evil-smelling membrane over the local lesion (Herrlich *et al.* 1965).

Foetal vaccinia, of which the naked-eye lesions are mainly on the skin, will be dealt with later (pp. 257-61).

22

ABNORMAL SENSITIVITY OF PATIENT: LOCAL OR GENERALIZED TUBERCULOSIS AFTER BCG OR VOLE BACILLUS VACCINES OR TUBERCULIN

INOCULATION TUBERCULOSIS

THIS CHAPTER is concerned with the ill effect of vaccines used for the prevention or treatment of tuberculosis. Attention has already been drawn in Chapters 9 and 10 to the occurrence of tuberculosis in persons who have been injected with other vaccines delivered by contaminated syringes. Four such incidents have been described—the Ring incident of 1936 in Ireland associated with the injection of diphtheria prophylactic (see p. 120); the Japanese incident of 1941 associated with the injection of TAB vaccine (see p. 133); the Lanarkshire incident of 1943 associated with the injection of APT (see p. 130); and the Japanese incident of 1948 associated with the injection of pertussis vaccine (see p. 134).

In addition must be mentioned the numerous cases described by Debré and his colleagues in France (see p. 122) and the 152 cases described by Mihov in Bulgaria (see p. 123); and lastly the three cases in Vienna after the injection of 'convalescent' measles serum in which the tubercle bacilli may have been present in the blood of one of the donors or may have come from a contaminated syringe (see p. 106). (See also p. 66.)

It is interesting to note that in Mihov's series of cases early toxic symptoms preceded the appearance of allergy by several weeks, suggesting that the incubation period in tuberculosis is not coterminous with the pre-allergic period.

Local or regional tuberculosis after BCG vaccine

The Bacille Calmette-Guérin (BCG) is a strain of tubercle bacillus of bovine type that has become practically avirulent as the result of several years' subculture on a glycerol bile potato medium. Calmette found that it could be injected into man and animals without causing more than a small retrogressive lesion, and that its presence in the tissues led to the development of tuberculin sensitivity (for references, see Rosenthal 1957).

It was first used by Weill-Hallé and Turpin (1925) in France for the vaccination of infants, and has been increasingly employed since then. By 1957 over a hundred million persons in different parts of the world had been vaccinated with this organism. In the early stages it was given by the mouth in three doses during the first ten days of life, but this method was found to be not very effective in the stimulation of allergy, and was replaced by subcutaneous, intracutaneous, or cutaneous inoculation. Today the intracutaneous or one of the multiple methods of cutaneous inoculation is generally practised.

Lymphadenitis

After intracutaneous injection of about 0.1 mg a local nodule forms in 4-5 weeks and breaks down after 6 weeks. The small ulcer that results usually heals in a few weeks to two months leaving an insignificant scar

(Holm 1946). The local lesion is generally accompanied by a mild non-suppurative enlargement of the regional lymphatic nodes.

In infants, however, particularly young infants, the regional nodes often swell considerably, suppurate, and in the course of a few months perforate the skin and discharge pus that *i(* either sterile on culture or contains a few organisms indistinguishable from BCG. The frequency with which this happens is determined principally by the age of the infant, the size of the dose, the degree of avirulence of the strain, the proportion of living to dead bacilli in the vaccine and the site of inoculation. Hsing (1954), for example, in Taiwan, found that the proportion of vaccinated persons showing perforated lymphatic glands was 23.3 per cent in the newborn infant, 2.3 per cent in infants aged 1 month to 2 years, and nil in children of 3-6 years. The discharge from perforated glands lasts for several months and not infrequently for over a year (Heaf 1955, Report 1955*b*).

Stoppelman and Drion (1956) in Holland, who examined children 3½ years after they had been vaccinated as infants with different doses of BCG, found that of those who had been given the largest dose—two intracutaneous injections each of 0.1 ml—26.6 per cent had had suppurating regional lymphatic nodes, as opposed to 7.1 per cent of those receiving two doses of 0.05 ml, and 3.1 per cent of those receiving two doses of 0.03 ml. In many cases suppuration did not begin for ten months or longer after vaccination, and in 7 out of 1608 children suppuration was still present after 3½ years.

Likewise Guld and his colleagues (1955) at Copenhagen, who observed infants six months or more after they had been vaccinated at birth with different doses of BCG, found that 25 per cent of those given the largest dose—0.15 mg—were suffering from enlarged or perforated axillary lymph nodes, 10 per cent of those given 0.075 mg, less than 5 per cent of those given 0.0375 mg, and only occasional infants among those given smaller doses. (For variations in the virulence of different strains of BCG, see Jensen 1946, Holm 1946, Report 1955*b*)

In France, Mande, Fillastre and Herrault (1958) noted the occurrence of suppurating lymphadenitis in 96 out of 29 898 children (0.32 %), most of whom were under five years of age but some of whom ranged from five to twenty years. In infants the percentage was 1.24. The authors formed the conclusion that the incidence increased with increase in dosage; and they recommended that large doses should be avoided. In 29 290 French recruits Foliguet (1966) recorded an incidence of suppurating lymphadenitis of 0.01 per cent. He remarks that a general febrile reaction may follow about four weeks after vaccination with BCG accompanied by asthenia and loss of weight; it is commonest in children and seldom occurs after 20 years of age.

The inflammation of the lymphatic nodes, which is not always confined to the regional nodes, is sometimes referred to as *BCG-itis.* This is seen not only after intradermal, but also after subcutaneous and cutaneous vaccination (Blanch, Blanch and Scremini 1948). Another manifestation of BCG-itis is erythema nodosum, which very occasionally develops 6-8 weeks after vaccination (Kostic-Yoksic 1951, Report 1956*a*)

Lupus vulgaris

An uncommon local complication of vaccination is *lupus vulgaris* (Marcussen 1954, Høvding and Wetteland 1956). Ustvedt (1956) said that about 30 cases had been reported, half of them in Scandinavia; but, as only

a very small proportion of vaccinated children are followed up and as lupus may not appear for several months, it is probable that its incidence has been underestimated. In most cases an extensive local lesion has persisted at the site of inoculation and increased during months or years, gradually becoming transformed into recognizable lupus; and in most cases the regional lymphatic glands have been enlarged, with or without suppuration.

Generalized tuberculosis after BCG vaccine

There is reason to believe that some of the injected organisms in the vaccine rapidly reach the lymph nodes and are distributed by the circulating blood to different parts of the body. Usually this haematogenous dissemination is of no importance, or gives rise only to small retrogressive foci of inflammation in the viscera or skeleton (Ustvedt 1956). But occasionally the organisms produce serious lesions that may prove fatal. Five deaths occurred from this cause before 1956. Since then eight others have been recorded (Carlgren *et al.* 1966).

It may be well to give a brief history of each of the five cases. Before doing so, however, it should be pointed out that four out of the five were observed in Sweden, Norway and Denmark. Though vaccination with BCG has been extensively employed in these countries, the total number of children vaccinated has formed only a small proportion of those vaccinated in other parts of the world. The presumption, therefore, is that numerous other deaths must have occurred, but through lack of the close observation that is usual in Scandinavia they have not been recognized. Complications that may not be apparent for months after vaccination are far less likely to be ascribed to their true cause than those which come on within a few days. In the large international campaigns for BCG vaccination the children have not been followed up or examined medically at 6-monthly intervals for five years or so, and it is, therefore, impossible to estimate the amount of damage that has been done by the vaccine. All we can do is to assume that it has been greater than is indicated by the number of reported cases.

Case 1

This was described by Despierres, Viallier and Sabot (1951) in France. Infants were being vaccinated in a maternity home at Lyon by the scarification method on the 9th or 10th day of life. About one-half of those examined six weeks later suffered from BCG-itis, i.e. inflamed and sometimes perforated regional lymphatic glands. In one of these infants other glands—cervical, supraclavicular and masseteric—were affected as well. They contained abundant pus in which no organisms could be demonstrated. This infant became febrile, lost weight and died in three months. No post-mortem examination appears to have been made. Some authors reject this case on the ground of insufficient evidence but, in view of the inflammatory lesions that followed vaccination in many of the other infants, it seems more reasonable to regard it as an unusually severe and fatal case of BCG-itis than to assume that it was due to some entirely different cause.

Case 2

The case described by Hollström and Hård (1953) in Sweden was that of an infant girl vaccinated with BCG in the left thigh two days after birth. Six months later a painless lymphoma in the left groin was incised which

at nine months had become an abscess from which bacilli indistinguishable from BCG were cultivated. By this time she was stuporous, sub-febrile and emaciated. The illness ran a septicaemic course with high febrile paroxysms and increasing cachexia. The lymph nodes in the right groin, the axillae and the thorax became affected, undergoing enlargement, necrosis and ulceration. The infant died in 15 months. At autopsy the principal findings were generalized enlargement of the lymph glands, partly with caseous necrosis, and the presence of disseminated abscesses in most of the viscera. Material removed at biopsy shortly before death revealed histologically dense agglomerations of epithelioid cells containing vast numbers of acid-fast rods, suggesting, together with a negative Mantoux reaction, an overwhelming infection.

Case 3

This was the case of a boy in Denmark who was vaccinated with BCG at the age of seven years (Meyer and Jensen 1954). A fortnight later the local site was painful and the boy felt unwell. An axillary abscess formed in three months and was incised. The boy remained unwell and was febrile. Nine months after vaccination tubercle bacilli were found in stomach washings. Gradually large multiple swellings of lymph nodes formed in practically all parts of the body. Treatment with streptomycin and PAS was of no avail and had to be given up. The boy died after two years in extreme cachexia. Post-mortem examination revealed greatly enlarged lymph nodes in the mediastinum and widespread infiltration of the lungs but no actual tubercles. Histologically the lymph glands showed extensive caseation and necrosis with abscess formation and enormous numbers of tubercle bacilli. All the 13 strains of bacilli cultivated during life and after death proved indistinguishable from BGG.

Case 4

This occurred in Norway and is described by Thrap-Meyer (1954). It concerned a male student of 19 who was vaccinated with the product of the Norwegian BCG laboratory. About ten months later an abscess developed in the right axillary glands followed eight months later by abscesses in the chest wall. At 27 months he had an attack of serous meningitis. Then came further abscesses in the right kidney, the thoracic spine, the sterno-clavicular joint, the region of the trochanter, the pleura and the lungs. The patient died 5½ years after vaccination of general haematogenous tuberculosis. Organisms indistinguishable from BCG were cultivated during life from various abscesses, and from the sputum, pleural fluid, stomach washings, and urine (Oeding and Hesselberg 1954). The postmortem findings, described by Waaler and Oeding (1954), revealed the presence of widespread tuberculosis. Histologically there was a diffuse inflammatory reaction without the formation of any definite tubercles. Plasma cells were increased and there was a remarkable pyroninophilia. Cultures taken from the lung, spleen and abscesses in the spinal column and lymph glands yielded organisms of the same type as those obtained during life. This patient is said to have suffered from several infections during childhood and to have had a persistently high sedimentation rate. It was thought that he might have agammaglobulinaemia, but in fact an examination of his serum showed the presence of two to three times the normal amount of gamma globulin.

Case 5

A second case in Sweden was described by Falkmer, Lind and Ploman (1955). An infant boy was vaccinated in the thigh with BCG when four days old. The regional glands in the groin became enlarged at six months. Cough and fever followed four weeks later together with a gradual onset of dyspnoea and emaciation. X-ray examination showed large infiltrations in both lungs. Death occurred at eight months. At post-mortem there was ulceration at the vaccination site. The lungs were consolidated, and the left inguinal, retroperitoneal and mesenteric lymph nodes were enlarged and matted together. Histologically much of the substance of the lymph nodes was replaced by epithelioid cells. No tubercles or giant cells were seen, but there were fairly large numbers of acid-fast bacilli which on culture were indistinguishable from BCG. Smaller numbers of bacilli were found in the thymus, spleen, liver and lungs.

In these five cases the clinical picture appears to have been dominated by extensive involvement of the lymphatic glands. This is very similar to the acute form of tuberculosis that occurs in infants, and at all ages in primitive peoples, who are infected with virulent tubercle bacilli (for references, see Wilson and Miles 1964*b*). It denotes a very low degree of resistance to the tubercle bacillus. What the particularly low resistance of these five patients was due to, it is impossible to say; but, since we know that resistance is genetically determined, and may well show a normal distribution, it is perhaps not surprising that a few subjects should be met with whose resistance is at the extreme end of the curve. The existence of a minute proportion of such persons does not, of course, affect the general policy of vaccination, though from the complications that have been described it is clear that BCG is not entirely harmless to man. Other serious and often fatal ill effects have been attributed to BCG vaccination by James (1955); but, according to Calwell (1956), the evidence in nearly all the cases quoted by James is insufficient to prove that BCG was directly responsible.

BCG VACCINATION OF TUBERCULIN-POSITIVE PERSONS

The purpose of vaccination with BCG is to confer some degree of immunity on a person who has never been infected with a virulent tubercle bacillus; in other words to forestall a primary infection. Once primary infection with a tubercle bacillus has occurred, BCG has no useful function to perform. Indeed its use may be actually harmful.

For example, Levi-Valensi and Migueres (1951) tried the effect of vaccinating with BCG patients who were suffering from pulmonary tuberculosis. They used the scratch method. All the patients had an accelerated local reaction starting 24—36 hours later, reaching its maximum in 5-8 days, crusting over in a fortnight, and healing with detachment of the crusts in a month. Of the 31 vaccinated patients, 80 per cent had regional glandular reactions, 6 had fairly severe focal reactions, and 10 had general febrile reactions. The six focal reactions were characterized either by haemoptysis, laryngitis, radiological extension of the lung lesion, or an aggravation of the disease. The authors concluded that there is serious danger in giving BCG to patients with pleuro-pulmonary lesions, and that mass vaccination without previous tuberculin testing is inadvisable.

Unfortunately tuberculin testing in a mass vaccination programme is often far from perfect. For example, the tuberculin used may have lost some of its strength through exposure to light or other cause; the method of testing, such as the patch test, may be too insensitive, or the operation

itself may be inexpertly performed; or the result may be read incorrectly. Reporting on the intracutaneous vaccination of some 30 000 children in Yugoslavia, Kostic-Yoksic (1951) observed Koch's phenomenon in about 100 children who must already have been infected with the tubercle bacillus but who gave a negative result in the Moro tuberculin test. Apart from the severe, suppurating, ulcerative local reaction, there was fever lasting for 2-3 days, a rise in the sedimentation rate, a leucocytosis, and some loss of appetite and weight. In at least three of the children the Koch reaction was followed by reactivation of the primary lesion—hilar adenitis, or in one case cervical adenitis accompanied by phlyctenular conjunctivitis and scrofulodermia.

Like tuberculin (see below), BCG vaccine is liable to reawaken activity in a dormant lesion or to aggravate a latent active lesion. In this respect it corresponds to superinfection with virulent tubercle bacilli, though the degree of stimulation may be less.

The potential danger of vaccinating tuberculin-positive persons is often minimized by those responsible for conducting mass-immunization programmes, but these are really the least trustworthy guides. Their business is to vaccinate as many children as possible, not to follow them up and study the effect of vaccination upon them. Without careful supervision of the children over a period of preferably five years, it is impossible to know how many complications, recrudescences of latent disease and fatal infections result from vaccination. These have got to be looked for, in the same way as serum hepatitis coming on 3-5 months after an injection or a blood transfusion had to be looked for before its true incidence was appreciated.

THE ILL EFFECTS OF THERAPEUTIC TUBERCULIN

In 1890 Koch described a preparation, later referred to as Old Tuberculin, that could be used for the diagnosis and treatment of tuberculosis.

The subcutaneous injection of 0.01 ml of this product into a presumably normal man gave rise to no more than slight pains in the limbs and temporary malaise; but tuberculous patients reacted violently to such a dose. The reaction was of a triple nature: (a) a local reaction consisting of erythema and induration at the site of injection; (b) a focal inflammatory reaction affecting any unhealed tuberculous lesions in the body, and seen best in cases of lupus; and (c) a constitutional reaction starting in 4-5 hours, characterized by a rise in temperature to 39°, 40° or even 41°C and lasting for 12-15 hours.

According to Koch, the tuberculin killed the tuberculous tissue, which then sloughed off and was followed by healing. At a public conference he gave his audience a glowing account of the beneficial effect he had observed on patients he had treated and, abandoning his usual caution, ended up with the statement that incipient phthisis could be cured with certainty by use of the new material.

At the time of this pronouncement tuberculosis, both of pulmonary and non-pulmonary type, was rife in Germany and in other countries of Europe, and it is not surprising that thousands of patients insisted on having this latest treatment. Very little was understood of the mechanism of immunity in tuberculosis, and the potential danger of tuberculin was not appreciated. The result was that this substance was used indiscriminately for the treatment of all forms of tuberculosis, including the most advanced cases, in the confident expectation that a course of 1-2 months would bring about anatomical cure (see Löwenstein 1928).

The results were disastrous; severe focal and constitutional reactions followed. Latent foci were galvanized into activity; small spreading foci became intensely inflamed and extended rapidly; and in patients with advanced disease severe toxaemia resulted, tubercle bacilli from the inflamed lesions passed into the blood stream, and death occurred rapidly from generalized tuberculosis.

Manifestly a halt had to be called, but before this could be effective large numbers of patients had died as the result of tuberculin treatment and large numbers of others were worse than they were before. What the total number of casualties was no one can say, but there is no doubt that it was imposing.

Nevertheless Koch (1891, 1897) remained confident of the therapeutic virtues of tuberculin when this substance was given in the right dosage to the right kind of patient; and he spent much time in trying to improve on the original product.

There is no need to describe these attempts or the successive tuberculins that he made (see Topley and Wilson 1936). Tuberculin treatment continued to be used for many years by a dwindling number of clinicians. Dosage was strictly regulated. The treatment was thought to be most useful for stimulating chronic cases in which the lesions had become torpid showing neither advance nor progress towards recovery (see Burnand *et al.* 1922). Before the second world war it had been almost completely abandoned, and with the introduction of streptomycin, PAS and isoniazid at the end of the war its interest became merely historical.

COMPLICATIONS OF THE VOLE BACILLUS VACCINE

Compared with BCG the vole bacillus vaccine has not been used extensively. Much the same complications have attended its use, but the incidence of *lupus vulgaris* has been considerably greater. In Scotland, for example, Frew, Davidson and Reid (1955), who vaccinated 280 kindergarten and school children with the vole bacillus vaccine, found that after intradermal injection deep ulcers formed in all cases, accompanied by enlargement of the axillary glands; 45 per cent had axillary abscesses. In those vaccinated by multiple puncture, 5 per cent after one year and 15 per cent after two years were suffering from lupus at the site of inoculation. In the Medical Research Council's trial, likewise, in which vaccination by multiple pressure was used, lesions of lupus vulgaris developed in a number of the children (Report 1956*a*). Šula (1958) in Czechoslovakia, who used a specially attenuated strain of vole bacillus and administered the vaccine intradermally, saw only 72 complications, all glandular, among 32 772 persons vaccinated, and not a single case of lupus. It is doubtful whether the vole bacillus vaccine has any real advantage over BCG vaccine, and the frequency of lupus after use of the original strain is a serious drawback to it.

23

ABNORMAL SENSITIVITY OF PATIENT: COMPLEX REACTIONS AFTER OTHER VACCINES

Typhoid vaccine

AFTER SUBCUTANEOUS injection into the deltoid region typhoid vaccine not infrequently gives rise to a severe local and general reaction. This is presumably due to the toxicity of the vaccine and the sensitivity of the subject. Temporarily incapacitating as such reactions may be, I am not concerned with them here (see p. 15). Their severity may be reduced by the intradermal injection of a smaller dose without diminishing the immune response (Siler and Dunham 1939, Miles 1958, Barr *et al.* 1959).

Besides these, general reactions of a different nature may occur. Some of these are anaphylactic, some encephalitic, some neuritic, and some provocative and are dealt with in the appropriate sections. There are others, however, that are more difficult to classify. The following case histories are taken from records collected at the Ministry of Health during the years 1943-6.

Jaundice and liver damage

Six soldiers suffering from chronic gonorrhoea were treated by intravenous injection with TAB vaccine. All six suffered from jaundice coming on in two days. In two of them the jaundice was accompanied by fever and vomiting. Five of the six recovered within five days, but the sixth died six days after injection. At autopsy the liver was found to be severely damaged without, however, true necrosis.

In another case, occurring after prophylactic injection by the subcutaneous route, the patient suffered from bleeding from the mouth 16 hours later followed by collapse and death in 23 hours. At autopsy the liver was found to be enlarged and pale.

The occurrence of transient jaundice after TAB vaccine was noted occasionally by Robertson and Leonard (1956) in Royal Air Force recruits.

Cardiovascular reactions

Eight cases fell into this category. Two of them were fairly mild; the patients suffered from headache, syncope and respiratory distress coming on 1-1½ hours after an intramuscular injection of TAB; both recovered.

The remaining six cases were all fatal. The history was of malaise, vomiting, praecordial pain and collapse starting 1½-5 hours after injection, followed by death 4¾-7 hours after injection. Post-mortem examination revealed the presence of an enlarged heart, with sometimes acute dilatation of the right side, and oedema of the lungs. A persistent or enlarged thymus gland was noted in three of the subjects. In all six cases, death appeared to be due to cardiac failure.

A somewhat similar case occurred in a soldier who was given an intravenous injection of TAB vaccine and was found dead in bed at 7.30 a.m. the following day. This man had had a previous injection two days

before the fatal one, and it is conceivable that this case was an example of the Sanarelli-Shwartzman phenomenon (see p. 222).

A curious case, reported by Meyer (1919), was that of a 19-year-old recruit in the German Army who received the second of two typhoid vaccine injections in his left arm on a Saturday. He remained perfectly well for the next two days. On Monday night he went to bed, but awoke after a short sleep complaining that he felt unwell and could not breathe. He sprang out of bed and fell unconscious on the floor. By the time the doctor arrived he was dead. Autopsy revealed the presence of oedema of the glottis and of the superficial and deep cellular tissue of the neck and mediastinum on the left side, great hyperplasia of the follicles of the tongue, intestine and mesenteric lymph glands, hyperaemia and oedema of the brain, and an enlarged thymus gland. Death was regarded as being related to status lymphaticus. According to Meyer (1919), Askanazy at a conference reported the death from myocarditis of a 22-year-old soldier four days after his first typhoid vaccine injection.

Other cardiovascular reactions, such as cutaneous haemorrhages, pancytopaenia, myeloblastic reactions of the bone marrow, and death due to myeloid insufficiency have been observed by various workers (Report 1960*c*).

Arthropathies

These were observed not infrequently by Robertson and Leonard (1956) in Royal Air Force recruits given TABT injections. They were often difficult to distinguish from rheumatism. Sometimes the joint symptoms subsided rapidly and at others they persisted for a long time. In a few patients acute rheumatism supervened. Masko (1916) in Hungary, among other reactions after Besredka's typhoid vaccine, reported on nine cases of rheumatic arthritis clearing up within a week.

Disturbances of the reticulo-endothelial system

Robertson and Leonard (1956) noted among their RAF recruits (see above) various disturbances of the reticulo-endothelial system, particularly splenic and less often hepatic enlargement. Together with arthropathies they affected about 0.25-0.3 per cent of the 200 000 recuits injected. In Budapest, Masko (1916) observed 61 serious general reactions among 3000 soldiers given Besredka's typhoid vaccine. Of the 61, four suffered from nephritis, 35 from severe diarrhoea, 11 from typhotoxicosis, and two from enlargement of the inguinal glands. Which of these were due to disturbance of the reticuloendothelial system it is difficult to say, but they may be included under this general heading.

Summarizing the complications of typhoid vaccination, Raettig (1952) says that subcutaneous injection of the vaccine may activate latent infections with tuberculosis, malaria, herpes, poliomyelitis and polyarthritis (see p. 265), and be followed by severe disturbances of the nervous and the circulatory systems, particularly in older persons. For further documentation on the numerous unfortunate sequelae of typhoid vaccination, reference may be made to the article by Baerthlein (1931) and to the monograph by Raettig (1952).

Pertussis vaccine

The occurrence of convulsions and encephalitis after whooping-cough vaccine has already been described (p. 195). Apart from these particular

neurological sequelae, other reactions, some of them probably of nervous origin, are on record.

Madsen (1933) recorded the sudden death of a premature infant after its second dose of pertussis vaccine. Sako, Treuting, Witt and Nichamin (1945), though reporting mainly on abscess formation after pertussis vaccine, include one case of angioneurotic oedema of the eyelids and lips associated with transient anuria, and two cases of vomiting, diarrhoea and convulsions. Hopper (1961), in a series of 1700 infants injected with pertussis vaccine, reported that 40 of them were subsequently ill. Some of these infants had merely severe local and general reactions, but others suffered from generalized eczema, a generalized macular rash, persistent vomiting, persistent uncontrollable screaming, or collapse. The reaction was usually evident within half an hour to four hours after injection, though eczema took a few days to develop.

Uncontrollable screaming, coming on within an hour or two of the injection and lasting for up to 24 hours, is also recorded by Forrester (1965). The same author says that during the previous few years several infants had been admitted to hospital under his care who had collapsed and become pale, shocked and apparently lifeless soon after injection with a combined vaccine containing pertussis bacilli. Other reactions, mainly of the encephalitic and provocation type, are reviewed elsewhere (see pp. 199, 270).

There is no doubt that pertussis vaccine is one of the most toxic vaccines in current general use. This statement rests on both published and unpublished evidence. In the pertussis vaccine trials carried out under the Medical Research Council (Report 1959*c*) about 70 per cent of children at Liverpool suffered from local, general, or local and general reactions.

Numerous reports are at hand of untoward reactions after vaccination with DPT. For example, the Ministry of Health's files for 1963, 1964 and 1965 contain letters from medical practitioners and medical officers in all parts of England and Wales complaining of untoward reactions to the triple DPT vaccine or the quadruple DPT poliovaccine. The reactions include anorexia, fever, irritability, prolonged crying or screaming, vomiting, collapse, stiffness of the neck, drowsiness, and epileptiform convulsions. Much other evidence points to the frequency of severe reactions after these vaccines. There is reason to believe that the pertussis fraction is the toxic element responsible in this combined vaccine.

An unusual fatality after pertussis vaccine was recorded in **a** man of 45 who was being hyperimmunized in order to provide antiserum. He was given seven injections in 6 weeks. Two months later he received an eighth injection. A week after this he suffered from fever, night sweats, arthralgia and adenopathy. Later came occasional haemoptysis and cramping abdominal pains. His general condition deteriorated and he died in about three months. Death appeared to be due to progressive renal failure secondary to chronic diffuse vasculitis. At post-mortem the medium and small arteries were affected as well as the arterioles and veins in the lungs, heart, genital tract, testis, adrenals and kidneys. Numerous ante-mortem thrombi were found in the intrarenal arteries and veins. Bishop, Carlton and Sanders (1966), who describe this case, regard it as one of hypersensitivity angiitis.

Stock vaccines

Hektoen and Irons (1929), who sent out a questionnaire **to** American physicians on the use of stock vaccines for therapeutic purposes, received

1261 replies, along with others from a group of tuberculosis specialists. The stock vaccines used consisted of mixtures of organisms such as streptococci, influenza bacilli, or typhoid and paratyphoid bacilli. Untoward, harmful or dangerous reactions were reported by 140 of the 1261 physicians and by 25 of 258 others. The reactions ranged from severe general reactions characterized by high fever, tachycardia and prostration to fatal reactions characterized by collapse, syncope and death. Twelve deaths were reported as the result of the subcutaneous injection of stock vaccines prophylactically or therapeutically. Five of these were due to the activation of latent tuberculosis (see p. 278); of the remaining seven, four died within a few hours of circulatory collapse or pulmonary embolism, and three from infection.

Stock vaccines were also held responsible for 17 cases of asthma, one of which proved fatal.

According to unpublished records of the Ministry of Health, collapse and death from circulatory failure has occasionally been observed after the use of other vaccines, such as those against dysentery and scarlet fever.

Yellow fever vaccine

Sorel (1936), in French West Africa, describing the vaccination of 5699 persons in 1934 and 1935 with the Sellards-Laigret vaccine, says that two forms of undue reaction were observed—predominantly visceral and predominantly nervous. The nervous reactions have already been described (p. 56). The visceral reactions came on about the 6th day and varied in intensity from slight to severe. The severe reactions were characterized by aching of the limbs, severe fronto-orbital headache, pains in the neck and back, pain on pressure of the eyeball, a strange sensation in the throat, fever up to 40°C lasting for several days, and profound asthenia lasting often for several weeks. According to Macnamara (1953), visceral reactions accompanied by jaundice, vomiting and albuminuria coming on some days after vaccination, were rare after the French vaccine.

Rabies vaccine: phenol shock

The nervous complications following the use of rabies vaccine have already been described. Apart from local reactions, an unusual complication is that of phenol shock. This results from the injection of a phenolized vaccine into a blood vessel. It is characterized by acute circulatory collapse accompanied by profuse sweating, severe pains in the head, loss of consciousness, and a metallic taste in the mouth. With rest, fresh air and oral administration of a stimulant, the patient gradually recovers (Gildemeister 1965).

OTHER MISCELLANEOUS REACTIONS

Nephropathy

Baylon and Bernard (1966) review the literature on the occurrence of nephropathy after vaccination and record 35 cases of their own seen between 1952 and 1964 in the French Army. Most of these cases came on after the French triple vaccine against diphtheria, tetanus and typhoid-paratyphoid bacilli (DTTAB). They estimate the incidence at about 1 in 1000 inoculations, but say that many cases will be missed unless routine examination of the urine is carried out for a week or two after injection. They recognize two main forms. The early cases come on a few hours after inoculation and are characterized by a sudden onset with fever, shivering, headache and sometimes circulatory collapse. The renal

manifestations are haematuria and proteinuria. Cure is generally rapid but relapses may follow further inoculations. The late cases have an insidious onset one to two weeks after inoculation. The main features are oedema, raised blood pressure and blood urea, and proteinuria with sometimes microscopic haematuria. Most of the cases pass on to chronic renal insufficiency.

Numerous other reactions to various vaccines might be described, such as the eye lesions—neuroretinitis, keratitis, optic atrophy and blindness among others—that have followed smallpox vaccine, TAB or DPT vaccines (see Report 1965*b*). These are all very uncommon sequelae. Their real incidence is not known, and the part played by the vaccine in their causation is often doubtful.

Again there might be added the occurrence of malignant change in smallpox vaccination scars, of which Goncalves (1966) described one and found records of seven others in the literature.

24

INDIRECT EFFECTS: DAMAGE TO THE FOETUS

OF THE INDIRECT effects of vaccination may be mentioned damage to the foetus. Our information on the subject is scanty and contradictory and, apart from vaccinia, is mainly negative.

Foetal vaccinia

The occurrence of foetal vaccinia is well attested, though its frequency is open to discussion. Greenberg (1948), for example, concluded that congenital defects in the infant were no more numerous in the offspring of mothers who had been vaccinated during pregnancy than in those who had not, even when the vaccination had been performed during the first three months of pregnancy.

Lynch (1932) likewise concluded that vaccinia seldom influenced the *course* of pregnancy; but on the other hand, in an extensive review of the literature, he was able to collect numerous cases in which a foetus or premature infant was born with a generalized bullous eruption. In most of these cases the mother had been vaccinated because she had been exposed to smallpox, and it was, therefore, impossible to say whether the eruption on the foetus was caused by the variola or the vaccinia virus. A case of his own which he quoted, however, was undoubtedly one of generalized vaccinia.

Congenital abnormalities

Bellows, Hyman and Merritt (1949) followed up 893 pregnant women, of whom 720 were vaccinated at some time during pregnancy and 173 were not. The infants were examined at birth for congenital abnormalities, and again at 6 and 12 months both for abnormalities and for their physical and mental development. The results are given in Table 10.

The authors concluded that the difference between the incidence of abnormalities in infants of vaccinated and unvaccinated women was insignificant. The numbers were not large; and perhaps too much attention should not be paid to the difference between 2.3 per cent in the unvaccinated and 3.1 per cent in the vaccinated group, but there is a suggestion that the incidence of abnormalities may have been higher in the infants of vaccinated than of unvaccinated mothers.

TABLE 10. Congenital malformations in infants of mothers vaccinated or not during pregnancy. (Bellows, Hyman and Merritt 1949)

Vaccination state	Total pregnancies	Number of congenital abnormalities	Percentage of congenital abnormalities
Vaccinated: no reaction	149	7	4.7
Vaccinated: accelerated reaction	210	8	3.8
Vaccinated: primary take	361	8	2.2
All vaccinated	720	23	3.1
Not vaccinated	173	4	2.3

Much the same conclusions were reached by Abramowitz (1957) in Capetown and by Bourke and Whitty (1964) in Dublin.

On the other hand, MacArthur (1952) in Glasgow, who investigated 203 pregnancies in which the mother was vaccinated immediately before or during pregnancy, found a highly significant increase in foetal mortality among women vaccinated during the first three months of pregnancy. His findings disagree with those of Lynch (1932) and Greenberg (1948).

The available figures for the incidence of congenital abnormalities in the foetus are collected and summarized in Table 11. It will be seen that, apart from Greenberg's figures, there is a consistent tendency for congenital abnormalities to be commoner in the offspring of vaccinated than of unvaccinated mothers. If figures were available for successful primary vaccinations only, the difference might be greater.

TABLE 11. Incidence of congenital malformations in the foetus after maternal vaccination during pregnancy

Author	Vaccinated			Not vaccinated		
	Cases	Congenital abnormalities		Cases	Congenital abnormalities	
		No.	Per cent		No.	Per cent
Greenberg (1948)	2791	11	0·39	1949	15	0·77
Bellows *et al.* (1949)	720	23	3·1	173	4	2·3
Abramowitz (1957)	1121	24	2·1	201	3	1·5
Bourke and Whitty (1964)	114	3	2·6	453	3	0·7
	4746	61	1·29	2776	25	0·90

Generalized vaccinia of the foetus

The occurrence of generalized vaccinia in the foetus has now been reported by a number of different workers. Table 12 lists eighteen cases.

TABLE 12. Reported cases of generalized vaccinia of the foetus

Author	Stage of pregnancy vaccinated (weeks)	Interval between vaccination and delivery (weeks)
Lynch (1932)	24	4
MacArthur (1952) MacDonald and MacArthur 1953†	12	11–12
Wiersum (1956)	21–4	6
Wielenga *et al.* (1961)	18	9
Tucker and Sibson (1962)	13	9
Entwistle *et al.* (1962)	19	4
Kropholler and Voorhoeve-den Hartog (1962)	15	7
Friart (1963)	22 *c.*	8‡
Hood and McKinnon (1963)*	before 13	?12
Killpack (1963)	12	9
Lycke *et al.* (1963)	23	5
Naidoo and Hirsch (1963)	22	8
Tondury (1963, 1964)†	7–8	11–12
Tondury and Foukas (1964)	6	12
Waddington *et al.* (1964)	19	4
Waddington *et al.* (1964)	22 *c.*	10 *c.*‡
Green *et al.* (1966)	24	6
	14	4

* Mother was vaccinated during the first 3 months of pregnancy and aborted at 4½ to 5 months.

† The figures given for the interval between vaccination and delivery—11 and 12 weeks—differ in the two accounts of the same case.

†† Survived.

It will be seen from the table that most of these have been described in quite recent years, suggesting that many previous cases must have been left unreported. That this is not unlikely is clear from the report by Friart (1963) who, when he was reporting his own case, was told by Dr Straetmans, Chef du Service de la Maternite de IMC d'Ixelles in Belgium, that he had seen about 20 women who had been vaccinated during the third trimester of pregnancy and that, of these, two had given birth to infants covered with a vaccinial eruption.

Among the cases listed in Table 12 the time of vaccination of the mother varied from 6 to 24 weeks. Six of the cases were in the offspring of mothers vaccinated during the first three months of pregnancy and twelve between 3 and 6 months. The fact that in no fewer than twelve of the cases the mother had been vaccinated during the second trimester casts doubt on MacArthur's conclusion that vaccination during the later months of pregnancy carries with it very little risk. This is borne out by the observations just quoted of Straetmans, who observed two cases of vaccinia in the infants of mothers vaccinated during the third trimester.

In all cases pregnancy came to an end before normal term; and, though in a few cases the foetus was born alive, nearly all died soon after birth. Indeed only two survived. Most of the foetuses were macerated when born.

That vaccinial infection was responsible for the lesions on the foetus was demonstrated beyond doubt in some of the more recent cases in which the vaccinia virus was grown from the lesions on the chorio-allantoic membrane of the developing chick embryo or demonstrated in the placenta by immuno-fluorescent staining (Wielenga *et al.* 1961, Entwistle *et al.* 1962, Naidoo and Hirsch 1963, Green *et al.* 1966).

On the limited evidence available it seems justifiable to conclude that vaccination of the mother at any time during pregnancy is not without risk to the foetus and that, when generalized vaccinia leading to maceration of the foetus occurs, abortion or premature birth is likely to follow. The risk of foetal complications, however, appears to be limited to primary vaccination. Provided that there is certain evidence of previous successful vaccination, there is no reason why revaccination should not be undertaken (see Bourke and Whitty 1964).

FOETAL DAMAGE CAUSED BY OTHER VACCINES

Though damage to the foetus as evidenced by abortion, premature birth, stillbirth, or congenital malformations is not uncommon in certain diseases, there is very little evidence, apart from vaccinia, that it is caused by vaccines.

According to Bass (1959), the virus of *measles* can traverse the placenta, infect the foetus and cause spontaneous abortion, but does not give rise to abnormalities in the foetus. Fox, Krumbiegel and Teresi (1948), however, think otherwise. So also does Swan (1951), who stated that in 62 recently reported cases of measles in pregnancy there were 47 normal infants, 1 premature infant, 3 abortions, and 11 infants suffering from congenital defects.

Information on *mumps* is likewise discrepant. Swan and Tostevin (1946) credit it with the ability to cause defects in the foetus, and Froewis (1960) quotes figures from the literature to show that 16-22 per cent of maternal infections in the first trimester result in injury to the foetus; but Fox, Krumbiegel and Teresi (1948) found no reason to believe that it gave rise to foetal abnormalities. Swan (1951) analysed a series of 93 cases of

mumps in pregnancy, and found that there were 68 normal babies, 2 premature babies, 1 stillbirth, 2 miscarriages, 2 abortions and 18 infants suffering from congenital abnormalities.

Rubella virus is the most destructive of the viruses, leading often to death of the foetus or to congenital abnormalities affecting particularly the eye, the ear, and the heart. The *coxsackie virus* may cause myocarditis or meningo-encephalitis. The *cytomegalic virus* may cause hepatosplenomegaly, jaundice, and various blood changes.

The poliomyelitis virus may invade the foetus and, according to both Fox, Krumbiegel and Teresi (1948) and Töndury (1960), may be responsible for congenital abnormalities. Gifford and Hullinghorst (1948) analysed 170 cases of poliomyelitis during pregnancy. The maternal mortality was 19 per cent and the foetal 26 per cent. No evidence was found of intrauterine transmission of infection to the foetus, and no mention is made of foetal abnormalities. Swan (1951), who analysed 195 cases, reported 141 normal infants, 31 deaths just before or after birth, 17 abortions or miscarriages, and 6 cases of congenital abnormalities in the foetus. Flamm (1959) collected records of 30 undoubted cases. In a few of these the foetus died during the third or fourth month of pregnancy; in the remainder the disease was present at birth or the poliovirus was isolated from the living or dead infant. There seems little doubt, therefore, of the potentially harmful effect of maternal poliomyelitis on the development of the foetus.

According to Bass (1959) the virus of *infectious hepatitis* does not appear to damage the foetus, but the figures given by Froewis (1960) contradict this. *Varicella* seems to be harmless, though Swan (1951) quotes 6 cases of congenital chickenpox occurring within 1 to 9 days of birth.

Influenza is in a peculiar category because of the great variability in its severity. In the pandemic of 1918-19 Harris (1919) says that pregnancy was interrupted through abortion or premature labour in 468 out of 1211 cases; and Bland (1919) in Philadelphia, analysing 200 cases occurring at the height of the outbreak in October 1918, reported that no fewer than 98 died. There were only 49 babies delivered and, of these, 25 were born dead or died within a few hours or days. Congenital abnormalities do not appear to have been observed. Bull (1945) remarks that pregnancy is often interrupted, particularly when influenza occurs in the later months. These findings are quite different from those of the milder forms of influenza that have occurred of more recent years. Nevertheless Töndury (1960) brings evidence to suggest that influenza may lead to spontaneous abortion and that the virus is responsible for submeningeal and ventricular haemorrhages in the foetus.

Of the bacteria, *listeria monocytogenes* is probably the most harmful, giving rise to metritis in the mother followed by premature expulsion or death of the foetus, and sometimes to generalized infection of the foetus—granulomatosis infantiseptica.

Of the spirochaetes, *Treponema pallidum,* as is well known, may infect the foetus and give rise to widespread disease.

Of the protozoa, *Toxoplasma gondii* may produce disease in the foetus resulting in convulsions, jaundice, general adenopathy, ocular palsies and hepatosplenomegaly in the infant (Bass 1959).

Against very few of these diseases, however, are vaccines used. The two main exceptions are poliomyelitis and measles. Extensive use of living attenuated poliomyelitis vaccine has so far failed to show that vaccination during pregnancy has any deleterious effect on the offspring.

It is true that Just and Bürgin-Wolff (1963) recorded three abortions and three stillbirths among 29 women who had been immunized with Sabin's attenuated vaccine during the first three months of pregnancy, but such figures are too small to be significant; moreover attempts to isolate the virus from the placenta were uniformly-unsuccessful. Experience with living attenuated measles vaccine has been much less, but again no harm to the foetus seems to have resulted from its use during pregnancy.

On general grounds it may be wise to refrain from vaccinating women with live poliomyelitis or measles vaccine during the first three or four months of pregnancy; and it is certainly wise to refrain from vaccinating a pregnant woman with smallpox vaccine during the first six months unless it is urgently called for in her own interest. The study, however, of infections in prenatal life is still in its infancy, and it may well be that further observations will lead to changes in our views on the advisability or otherwise of vaccinating pregnant women. For further information reference may be made to the monograph by Flamm (1959) and the Colloquium held in Vienna in May 1959 edited by Bieling and Flamm (1960).

25

INDIRECT EFFECTS: PROVOCATION DISEASE

WHEN A VACCINE is injected into the tissues during the incubation period of a disease or during the course of a latent infection it may bring on an acute attack of the disease. That is to say the incubation period is shortened, or a latent infection that might have given rise to no manifest illness is converted into a clinical attack. The two diseases in which this so-called provocative effect has been most studied are typhoid fever and poliomyelitis, but evidence exists to show that it may be operative in other diseases such as tuberculosis and rickettsial infections. Numerous factors, such as exposure to cold and wet, excessive fatigue, over-indulgence of various sorts, and certain chemotherapeutic agents, are credited with playing a similar role by lowering the resistance of the host to the causative bacterium or virus in question. Certain vaccines appear to have a similar effect, though probably more specific. Discussion of their mode of action will be reserved till later.

Provocation typhoid fever

Most of the observations made on the provocation of typhoid fever by vaccines come from Germany. Goldscheider and Kroner (1915) reported on the effect of inoculation on the outbreak of typhoid fever that struck the German Army in France in the autumn of 1914. They mentioned that, after the first and second injections at 8-day intervals, there was a negative phase in which severe cases occurred, but that after the third injection this no longer happened. Inoculation during the incubation period sometimes provoked a sudden and severe attack in those injected for the first or second time.

Basten (1915), likewise making observations in the German Army, stated that 28 men out of 707 who were receiving a course of three injections contracted typhoid fever shortly after injection. Examining the history of 202 patients suffering from typhoid fever he found that 34 had been taken ill within three days of inoculation. This figure excluded patients who were unwell at the time of inoculation and who might have contracted typhoid fever anyway.

Hünermann (1916), studying the protection afforded by typhoid inoculation, noted that an attack of the disease might follow immediately an inoculation in a latently infected subject. This provocative action was made use of in the German Army, in which it was recommended that, when typhoid fever broke out, all troops in contact with the sick should be reinoculated so as to reveal the existence of latent infections.

After the end of the first world war Basten (1920) described an outbreak of typhoid fever in December 1918 m the little town of Euskirchen situated in the occupied zone. Infection was spread partly by water and partly by contact. The British authorities insisted on vaccinating the civilian population with TAB, giving two doses at an interval of ten days. This was carried out in January 1919, when 14 343 persons aged 6-55 years out of a total population of 21 248 were inoculated. The outbreak was declining at the time, but immediately a fresh crop of cases appeared. After the first dose 16 persons went down at once with typhoid fever, and six immediately after the second dose; seven fell ill between the first and

second dose, and two 2 days after the second dose; that is, 22 cases followed immediately, and 9 a little later. Basten regarded all these cases as having been in the incubation period of the disease, which was shortened by inoculation. In his opinion the effect of this was to bring the outbreak to a more rapid end than would otherwise have been the case.

Jürgens (1927), reporting on the Hanover outbreak of 1926, said that many of the cases came on directly after typhoid vaccination. Friedberger (1927) likewise collected evidence to show that vaccination during the course of an outbreak was liable to activate latent infections and render them manifest; he quoted one instance in which the morbidity was higher among those vaccinated during an outbreak than among the unvaccinated.

During the Hanover water-borne outbreak of 1926, 117 000 persons were inoculated. The total number of typhoid fever cases was 2 200. Stroebe (1928), who was in charge of 800 patients, was of the opinion that 38 of them were cases of provocation disease—33 typhoid and 5 paratyphoid fever. Of the 33 typhoid cases, 13 came on after the first, 17 after the second, and 3 after the third injection; 14 of the 33 cases had their onset on the following day. In some the disease started abruptly with a rigor; in others the reaction to the vaccine passed insensibly on to the disease.

The provocative effect of TAB vaccine was commented on by Hench (1932) in the United States, who studied the reactions of about 2500 patients given the vaccine for the treatment of arthritis, vascular disease or other disorder. Fourteen of the patients had an unusual reaction consisting of appendicitis, cholecystitis, enteritis, pleurisy, pericarditis, iritis, glaucoma, adenitis, thrombosis, or renal insufficiency. The reaction was due not to the protein therapy itself, but to the awakening and unmasking of an underlying disease.

More recently Raettig (1950, 1959*a, b, c, d,* 1964) carried out a very careful study of provocation typhoid fever. In the first place he (1950) collected figures for the great typhoid fever epidemic of 1945-7 in Germany and found that, on the whole, inoculation lowered the case-fatality rate from 19.0 per cent to 11.2 per cent. In Greifswald, however, in August and September 1945, when inoculation was undertaken in the middle of an outbreak, numerous very severe and often fatal cases followed injection in a few hours to a few days.

Analysing the German figures more closely, Raettig found that the case-fatality rate in those contracting typhoid fever within 48 hours of injection was as high as in the uninoculated, i.e. about 19 per cent, whereas in those falling ill 3-21 days after injection it was only 10 per cent. Of the 1702 inoculated patients that fell ill within 48 hours of injection 35.2 per cent followed the first injection, 27.8 per cent the second, and 14.7 per cent the third, as against the expected proportion of 9.5 per cent for all inoculated cases. From these figures Raettig concludes that inoculation with typhoid vaccine, particularly the first injection, shortens the incubation period and increases the case-fatality rate. Whether it increases the attack rate is doubtful.

Raettig (1959a, *b, c, d)* next approached the subject experimentally. His general method was to infect mice orally with *Salmonella typhi-murium* and, during the incubation period of the disease, give them a subcutaneous injection of a killed *S. typhi-murium* vaccine. In his first paper (1959*a*) he showed that in these circumstances a number of inoculated mice died prematurely of mouse typhoid through provocation of the infection. In his second paper (1959*b*) he observed the same effect, though to a less degree, in mice inoculated with a non-specific vaccine

such as one of *S. enteritidis* or *Escherichia coli.* In his third paper (1959*c*) he brought evidence to show that inoculation had much the same effect in mice suffering from a latent infection as in mice inoculated during the incubation period. Further, he carried out an experiment in which a mouse infected with *S. typhi-murium* was introduced into a cage containing large numbers of healthy mice, half of which were injected with *S. typhi-murium* vaccine a few days later and half of which were left uninoculated. The results showed that the inoculated mice died more rapidly and in greater numbers than the controls. Finally he (1959*d*) showed that the provocation effect did not occur, or was very much weaker, when the mice were immunized before being exposed to infection.

In France Wolfromm and Bernard (1966) mention the striking case of five Mussulman recruits to the Army who went down with an attack of typhoid fever after inoculation with triple vaccine (DTTAB). They had recently arrived from the East and were probably typhoid carriers.

DISCUSSION

Brieger and Ehrlich (1893) were the first to describe the depressing effect of the injection of an antigen on the circulating antibody. They observed in fact that, in goats immunized with tetanus toxin, a further injection caused a fall in the antibody content of the milk. Ehrlich had made a similar observation some years earlier on the anti-ricin content of the blood of rabbits.

Almroth Wright (1901) found in man that after a dose of typhoid vaccine the bactericidal action of the blood often decreased for a time before rising; for this phenomenon he coined the expression *negative phase.* The immunological significance of this phase has long been under discussion (Ledingham 1937), and even now opinions remain divided (see Raettig 1964). The evidence, however, that has been adduced here, and the evidence that was more fully reviewed by Topley (1938), leaves little doubt of the reality of provocation disease, and suggests that the immunological disturbance caused by the injection of a vaccine is indicative of a genuine lowering of resistance during the negative phase.

Provocation disease can occur, of course, only when there is a latent infection or when the patient is actually in the incubation period. These two states are most likely to be met with during an outbreak of the disease in question. In an explosive outbreak of typhoid fever caused by contaminated water, milk, or food there are bound to be, at any one time, cases in the incubation period of the disease, and it is these that are most likely to be adversely affected by typhoid inoculation. In an endemic situation, on the other hand, patients in the incubation period are likely, at any one time, to be few, and the danger of provocation typhoid is much less. From a practical standpoint, therefore, it is probably wise to refrain from inoculating a population during the course of an epidemic, but to encourage inoculation of those living in an endemic area, such as labourers in mines or on plantations, and the rural population generally, as well, of course, as persons living under conditions of good sanitation who are travelling through or taking up residence in an endemic area, and are in danger of being exposed to infection.

Raettig and others have shown that in provocation disease the incubation period is shortened and the severity of the disease, as judged by the complication rate and the case-fatality rate, is increased. Evidence, however, that the attack rate in man is heightened is still incomplete, though experimentally in mice Raettig (1959*c*) found that latent infections were activated. No useful deductions can be drawn from a comparison of

inoculated and uninoculated persons during an outbreak of the disease, since the proportion of those in the incubation period will be much the same in each group. If, of course, there were many latently infected persons who were not in the incubation period, as happened in the outbreak described by Jones (1951) at Oswestry, and the proportion of patients who contracted the disease was greater in the inoculated than in the uninoculated, then the case would be proved, but so far no satisfactory observations of this nature appear to have been made. What is required is a study of latent infections in an endemic area; but even here the provoking action on persons who were latently infected might be counteracted by the immunizing action of the vaccine on those who were not yet infected. For the present we must leave the question unanswered, at least so far as typhoid fever is concerned.

Provocation poliomyelitis

The occurrence of neurological sequelae to the injection of sera and vaccines has already been discussed. The disease now to be considered, provocation poliomyelitis, appears to have a different aetiology and must therefore be considered separately.

Wilkinson (1937) recorded a very suggestive case of motor paralysis affecting all four limbs and many of the facial muscles coming on a week after the injection of APT into a year-old infant. Though the diagnosis was multiple neuritis, the absence of pain or any other sensory disturbance renders one of poliomyelitis more probable.

Martin (1950) in London drew attention to the relation between inoculation against diphtheria or pertussis and an attack of poliomyelitis when he described fifteen cases that he had seen between 1944 and 1949. Paralysis came on as a rule 7 to 21 days after injection and affected the left arm, into which injections are commonly made, four times as often as the right. Martin also collected records of 67 further cases occurring in England and Wales between 1941 and 1949. These presumably included some, if not all, of the 31 cases reported to the Ministry of Health during the years 1941 to 1946.

Interest in this relationship was greatly stimulated by the observations of McCloskey in Australia and of Geffen in London. McCloskey (1950) investigated 375 cases of poliomyelitis during an epidemic in Victoria in 1949, and found that 31 of the patients had been inoculated against diphtheria or pertussis, alone or in combination, within the preceding three months, all but two of them within the preceding 5-32 days. Paralysis was most frequent in the inoculated limb. A year later McCloskey (1951) published a second report in which he had increased his number of cases to 675. Of these, 53 patients, about whom exact information was obtainable, had received an injection of vaccine within three months of the onset of symptoms—40 of them within 28 days. He brought evidence that inoculation increased the severity of the paralysis, and that pertussis vaccine, alone or combined with diphtheria toxoid, was more potent in provoking paralysis than diphtheria toxoid by itself.

In London Geffen (1950) noted that in the 1949 epidemic 30 out of 182 paralytic patients under five years of age had been immunized against diphtheria, pertussis, or both within four weeks of contracting poliomyelitis. In all of these cases the limb last injected was paralysed; in another seven cases a different limb was affected. In 21 of the 30 cases combined diphtheria and pertussis vaccine had been used, APT in eight, and pertussis vaccine alone in one. Geffen calculated that the proportion of

children becoming paralysed after immunization was of the order of 1 in 1800. The interval between injection and the development of poliomyelitis was usually between 5 and 16 days (Geffen, Paterson and Tracy 1953).

The conclusion to be drawn from these various reports was greatly strengthened by the statistical analysis carried out by Hill and Knowelden (1950). Records were examined of 410 poliomyelitis patients under five years of age occurring in 33 administrative areas of England and Wales during 1949. In 164 of these a closely paired control child was available. Analysis revealed an excess of poliomyelitis cases in children that had been inoculated within the previous 28 days with APT, combined APT and pertussis vaccine, or pertussis vaccine alone. In these cases the arms were affected as often as the legs, and the left arm more often than the right. In those that had not been inoculated within a month the legs were affected 2-3 times as often as the arms. In the recently inoculated children the limb of injection was paralysed much more frequently than the corresponding limb in children not recently inoculated. Comparing the inoculation history in the cases of poliomyelitis with measles and 'birthday' controls, Hill and Knowelden found an excess of poliomyelitis cases in children inoculated within the previous month, suggesting that inoculation favoured the development of clinical paralytic disease. In most of the provocation cases the onset of paralysis was 8-17 days after inoculation.

The objection that the diagnosis of poliomyelitis was wrong in these provocation cases was ruled out by the isolation by MacCallum (1950) of the poliovirus from the stools of five children who had contracted paralysis 5-17 days after inoculation with APT or pertussis vaccine.

Further observations were made by numerous other workers in Great Britain and the United States during the next year or two. Banks and Beale (1950), for example, at the Park Hospital, London, noted that 14 out of 111 patients suffering from paralytic poliomyelitis had paralysis of a limb that had received one or more immunizing injections within the previous two months, mostly within the previous 9-14 days. The vaccines concerned were APT (4 cases), pertussis (1) and combined APT and pertussis (9).

In the United States Anderson and Skaar (1951) examined the histories of children under seven years of age who had suffered from poliomyelitis during the 1946 outbreak in Minnesota. Of 85 confirmed cases occurring within six months of an injection, 33 had had their most recent injection of diphtheria, pertussis or tetanus vaccine—mostly combined—within the preceding month. The injected limb was paralysed in 19 (58 per cent) of these 33 cases, whereas of the 52 cases coming on within two to six months the injected limb was paralysed in only 8(15 per cent). There was a suggestion that the first-month cases were more severe than those occurring later, and that injection was more likely to predispose to paralysis in the younger than in the older children. The interval between injection and the onset of illness in the 33 cases was mainly 5-19 days.

Greenberg, Abramson, Cooper and Solomon (1952) reached similar conclusions as a result of examining the inoculation histories of 1300 children of five years of age or under that had suffered from poliomyelitis in New York City in 1949 and 1950. A significantly greater proportion of children were paralysed in the injected limb when the last injection had been made within the preceding month than within the preceding 1-12 months. The ratio of leg to arm paralysis changed from about 3:1 to about 1:1 in those injected within the preceding month. The vaccines used were

those against diphtheria, pertussis and tetanus; no attempt was made to distinguish between the effect of single and of combined vaccines.

Korns, Albrecht and Locke (1952) studied the histories of 2137 poliomyelitis patients in New York State in 1950, along with those of 6055 members of the patients' households and 14 170 controls from adjacent households. They found that poliomyelitis patients gave a history of receiving an immunizing injection during the preceding two months about twice as often as did the control persons of similar age. Unlike previous observers, they could find no difference in this respect between patients immunized during the preceding month and the preceding two months. There was a close association between the site of injection and the site of paralysis. The severity of the paralysis was rather more severe in the immunized than in the non-immunized group of patients.

Working on the London County Council figures, Benjamin and Gore (1952) calculated that during 1949 the risk of contracting poliomyelitis was nearly four times as high in children of 9-24 months who had received an injection of combined diphtheria and pertussis vaccine within the previous six weeks as in a control uninoculated group.

Grant (1953) at Gateshead studied a small series of cases occurring in the south Tyneside area in 1952 and found that paralysis was more frequent in children who had been recently inoculated with APT or PTAP, alone or combined with pertussis vaccine, than in children not recently immunized, and that paralysis was commonest in the injected limb.

Finally a committee of the Medical Research Council (Report 1956*c*) undertook a special investigation in an endeavour to ascertain the degree of risk incurred by children submitted to immunization in England and Wales. Between 1951 and 1953 all cases of paralytic poliomyelitis in children under 15 years of age were personally investigated when the patients had had an injection of diphtheria or pertussis vaccine or had been vaccinated against smallpox within the preceding twelve weeks. Of the 355 paralytic cases falling into this category, 222 had completed a primary course of immunizing inoculations or had received a reinforcing dose. In 132 of these 222 patients paralysis had come on 1-28 days after inoculation, mainly in 11 to 17 days.

In certain areas of the country the medical officers of health kept a record of the number of inoculations given in welfare and school clinics. From these it was calculated that about 1 in 37 000 inoculations precipitated an attack of paralytic poliomyelitis. The evidence showed that the provocation effect did not last beyond a month, and that a series of inoculations had no cumulative effect. The frequency of paralysis was greatest after combined alum-precipitated diphtheria and pertussis vaccine and least with plain formolized diphtheria (FT) and diphtheria toxoid antitoxin floccules (TAF). Smallpox vaccine was without effect. More precisely, the incidence of paralytic poliomyelitis in children immunized within the previous four weeks was:

APT	3.4 per 100 000
PTAP	6.0 per 100 000
FT and TAF	1.4 per 100 000
Pertussis	1.9 per 100 000
Combined diphtheria and pertussis, alum-precipitated	8.0 per 100 000
Combined diphtheria and pertussis, without alum	6.5 per 100 000

Altogether it was estimated that in these areas about 13 per cent of paralytic cases in children aged 6—24 months were causally related to inoculation. A clear relation between the site of injection and the site of paralysis was demonstrated. No difference was found between the effect of subcutaneous and of intramuscular injection. These findings were substantiated by a modified investigation conducted in 1954 and 1955. While leaving the mode of action open to conjecture, the Report is in no doubt that inoculation genuinely predisposes to the occurrence of paralysis and does not act merely by determining the site of paralysis.

Experimental observations

When the occurrence of provocation poliomyelitis had been clearly demonstrated in man, a number of workers tried to reproduce the disease experimentally in animals. Though Melnick and Ledinko (1952) were unsuccessful, Bodian (1954), working with cynomolgus monkeys injected intracardially with the invasive type 1 Mahoney strain of poliovirus, obtained striking results. In such monkeys the normal paralytic rate was about 50 per cent, the initial paralysis being usually in the arm; but when the animals were given simultaneously an intramuscular injection into the right leg of gelatin, cortisone, penicillin, or alum-precipitated DPT vaccine the paralytic rate rose to between 70 and 90 per cent, the initial paralysis being usually in the right leg. The provoking effect was observed even when the injection of the virus was delayed for two weeks, but it dwindled rapidly after three weeks.

Dean, Cohen and Dalldorf (1951) obtained very convincing results working with the virus of mouse encephalomyelitis, which produces in mice a disease closely resembling poliomyelitis in man. They injected mice intracerebrally with the virus and subcutaneously into the left front leg with two doses of vaccine at a week's interval. The vaccines used were fluid pertussis, alum-precipitated diphtheria-tetanus toxoid with or without pertussis, and TAB vaccine. After pertussis vaccine alone or combined, the incidence of paralysis in the left front leg was seven times that among the control animals. Precipitated DT toxoid had less effect and TAB had none. The effect of the vaccine was to localize the paralysis in the injected limb and to shorten the incubation period; it had apparently no effect on the proportion of mice paralysed.

Findlay and Howard (1950), who infected mice intracerebrally with the Lansing strain of poliovirus and subsequently gave them an intravenous injection of TAB, diphtheria toxoid, or a mixed diphtheria-pertussis vaccine, observed that mice treated in this way became paralysed more rapidly and died earlier than infected mice that were left untreated.

Also working with mice, but using the mouse adapted MEF 207 strain of poliovirus, Raettig (1959*e*) found that even poliomyelitis vaccine was able to provoke an attack of poliomyelitis. He observed that Salk vaccine, when injected seven days after intracerebral inoculation of the poliovirus, increased the mortality as compared with that in control unvaccinated mice. But mice that had been previously immunized with Salk vaccine and were then given a fourth dose during the incubation period of the disease showed no such effect; in fact they had a lower mortality than the controls, suggesting that vaccination can protect against provocation poliomyelitis.

DISCUSSION

The reality of provocation poliomyelitis has been doubted by a few workers, or its risk minimized (Holt 1959), but the evidence in its favour is

sufficiently strong to convince most unbiased observers. Though the actual number of cases reported by any one observer is not large, they are extraordinarily concordant in their history. As Anderson and Skaar (1951) remark: 'Considerable attention must be attached to the fact of uniformity of results in a series of independent observations even though each may be small.'

The mode of action of the injected vaccine is open to doubt. The most probable explanation is that it acts like a fixation abscess and allows virus circulating in the blood stream to settle down at the site of injection and thence proceed via the nerve fibres to the spinal cord. The greater the irritating effect of the vaccine, the more likely is this to happen. In the Medical Research Council committee's (Report 1956*c*) experience, the most potent vaccines were combined diphtheria-pertussis vaccine, with or without alum, and PTAP. It is interesting to note that Ben-Efraim and Long (1957) found that these vaccines caused a higher degree of skin hypersensitivity in guinea-pigs to formolized diphtheria toxoid injected intracutaneously than did either FT or TAF, thus pointing to a close association between the sensitizing power of these vaccines in guinea-pigs and their ability to provoke poliomyelitis in man. The use of the milder prophylactic agents seems to carry with it much less danger of provocation poliomyelitis. Peach and Rhodes (1954), for example, in Canada could find no evidence of the occurrence of this disease among children who had been immunized with plain fluid DPT vaccine.

Irritating substances, other than vaccines, may predispose to paralysis. Thus Rosen and Thooris (1953) reported that in French Oceania at the time of an epidemic of poliomyelitis the attack rate in children under 15 years who were being given weekly intramuscular injections of a mixture of arsenic, bismuth and mercury for the treatment of treponematosis was over ten times as high as in children not receiving treatment. A similar provoking action was noted by Townsend-Coles and Findlay (1953) for quinine.

Bodian (1954) is of the opinion that the injection of vaccine acts, not by allowing the virus to enter the injured peripheral nerve fibres, but by causing a change in the blood vessels of the corresponding segment of the spinal cord that renders them more penetrable by the virus. Whatever the explanation may be, it seems clear that the provoking effect can be manifested only when the patient is in the incubation period of the disease or is suffering from a latent infection. In either instance there must presumably be a transient viraemia of greater or less duration. That this is common in poliomyelitis there is now no doubt.

Whether the vaccine merely localizes the paralysis in the injected limb or leads to an actual increase in the proportion of paralytic cases is an open question. Experimentally in mice infected with the encephalomyelitis virus Dean, Cohen and Dalldorf (1951) found no evidence that the injection of a vaccine increased the frequency of paralysis as a whole. On the other hand, Hill and Knowelden (1950) and the Medical Research Council's committee (1956*c*) interpreted their findings as indicating that it predisposed to the occurrence of paralysis, thus converting otherwise non-paralytic cases into paralytic ones.

Provocation poliomyelitis is a disease that is necessarily confined to countries in which the poliovirus is active. It is no longer seen in regions from which poliomyelitis has been virtually eliminated by vaccination. Where poliomyelitis is still prevalent, it is advisable to avoid elective vaccination against diphtheria or pertussis during the height of the

poliomyelitis season and, at all times, to use a simple fluid vaccine rather than one precipitated with alum or aluminium phosphate.

There is no reason to believe that oral vaccination with the attenuated poliomyelitis strains of Sabin has any provocative effect, as the inactivated Salk vaccine given parenterally was found by Raettig (1959*e*) to have in mice. The Sabin vaccine can therefore be given at any time of the year and, indeed, even during an epidemic of poliomyelitis. Again judged by Raettig's findings, persons immunized against poliomyelitis are unlikely to suffer from provocation poliomyelitis when injected with diphtheria or pertussis vaccines. The wisest policy therefore in a country in which poliomyelitis is endemic is to immunize all infants, preferably during the second six months of life, with the oral poliomyelitis vaccine, and then to vaccinate them against diphtheria, pertussis and tetanus at the end of the first and beginning of the second year.

Other provocation diseases

Provocation disease is an example of what Remlinger (1933) calls *biotropism.* By this he means the exaltation of the virulence of an organism under the influence of an administered medicament. Alternatively it would be truer to say a lowering of the tissue resistance, since the medicament acts more probably on the host than on the parasite. Remlinger himself observed the frequent relapse of *malaria* and the less frequent relapse of *tuberculosis* that occurs in patients treated with antirabies vaccine.

The activation of *tuberculosis* by typhoid vaccine given intravenously to a patient suffering from spondylitis was noted by Cecil (1935); and I personally have seen a similar activation of tuberculosis following an attack of undulant fever. One case of miliary tuberculosis coming on within a fortnight of the first dose of TAB and proving fatal in two months was reported to the Ministry of Health in 1941. As the result of a questionnaire issued by Hektoen and Irons (1929) to American physicians five deaths from tuberculosis were reported following the use of stock mixed vaccines and seven deaths following the injudicious use of tuberculin. In all these cases latent or mild tuberculosis had been wakened into activity by prophylactic or therapeutic vaccine treatment.

Various workers have noted the occurrence of an exacerbation in tuberculous patients injected with diphtheria toxoid; and this vaccine has also been held responsible for the reactivation of rheumatism and for the onset of an attack of serofibrinous pleuritis (see van Ramshorst and Ehrengut 1965).

The Ministry of Health have an unpublished record of a patient in whom miliary dissemination of BCG followed smallpox vaccination.

In mice suffering from a latent infection of some months' standing with *Mycobacterium fortuitum* Schaedler and Dubos (1957) noted that the intraperitoneal injection of killed BCG or pertussis vaccine disturbed the equilibrium and converted a latent or chronic infection into an acute and sometimes fatal disease. One of the most constant manifestations of this change was the appearance of a large microbial population in the liver, even though in normal mice *M. fortuitum* is rapidly cleared from the liver.

In some of the *rickettsial diseases* the parasite remains latent in the tissues for months or years and is then, for some reason, stimulated into activity to give rise to clinical illness. It is probable that Brill's disease results from some disturbing factor that allows the latent typhus virus to start active proliferation again. In the closely allied disease, *trench fever,*

Kostrzewski (1949) stated that in Weigl's laboratory in Warsaw, in which healthy lice were fed on volunteers, there was an increase in the number of carriers of *R. quintana,* i.e. of persons in whom this organism was found to be circulating in the blood, immediately after anti-typhoid injections had been made. He also recorded a case in which a woman who had suffered from trench fever five years previously had a relapse a few days after an antityphoid injection.

It seems clear that any latent infection, particularly when accompanied by transient bacteraemia or viraemia, may be wakened into activity by the disturbing effect on the tissue resistance of various factors, among which vaccines and certain medicaments are prominent. Ideally, vaccination against any disease should be preceded by a survey of the patient's medical history and a simple physical examination to detect any obvious signs of infection. Mass vaccination, in which this is impossible, is bound to be a hazardous procedure and is likely to be followed by undesirable consequences of one sort or another.

26

CONCLUSIONS

AS I STATED at the beginning, it is my purpose not to try and assess the net benefit or harm of using different vaccines and antisera, but to draw attention to the potential dangers of all vaccination procedures and to put them in their right perspective.

Routine immunization

The gradual conquest of the infectious diseases, in which protective immunization has played no small part, has posed the problem of how we are to prevent their recrudescence in the future. Are we to continue vaccinating against diseases that are no longer endemic, as Thomson (1966) envisaged in his recent Milroy lectures, or are we to run the risk of their returning in the course of time in their full epidemic strength?

The diseases I have particularly in mind as affecting Great Britain are diphtheria, poliomyelitis and smallpox. Provided they are properly prepared and used, the vaccines against diphtheria and poliomyelitis carry little danger, but this is not true of smallpox vaccine. The arguments for and against the use of this vaccine in a country where the disease is no longer endemic but is continually subject to the risk of reimportation are very nicely balanced; and it is here that a full knowledge of the various complications which may attend its use will be of help in reaching a decision on how far it should be included in a programme of routine immunization.

Much the same holds true of pertussis vaccine and, to a less extent, of BCG. Whooping-cough has now such a low mortality that the advisability of continuing vaccination against this disease must be seriously questioned, particularly when there is reason to believe that, as judged by the comparative mortality index before and after 1951, vaccination has played little part in bringing about its fall. Of the protective value of BCG we still have a great deal to learn but it seems clear that, in weighing up the arguments for and against its routine use, we need pay little attention to its danger so long as it is not used for the parenteral vaccination of very young infants or of tuberculin-positive subjects.

Measles presents an interesting example of a disease in which the mortality in relation to morbidity in Great Britain is extremely low but in which respiratory and neurological complications leaving behind them permanent damage are not infrequent. We know, as yet, little of the possible dangers of measles vaccines, but when we do learn about these we shall be in a better position to judge how far vaccination should be applied in practice.

Tetanus, of course, not being a contagious disease, falls into a different category. So far as we can see, tetanus will always be with us and immunization against it will always be required. The frequency of complications after the use of antiserum for passive immunization and their almost complete absence after the use of toxoid for active immunization point strongly to the desirability of actively protecting the population against this disease.

The inherent danger of all vaccination procedures should be a deterrent to their unnecessary or unjustifiable use. Vaccination is far too

often employed, especially in the developing countries, to avoid the tedious, troublesome and sometimes expensive process of improving personal and environmental hygiene. Admittedly there are some diseases of which vaccination is the only effective means of control, but even so it should not be introduced for routine use without making reasonably sure that it can be carried out under conditions that will more or less guarantee its effectiveness.

The diseases in which vaccination has played a dominant part in the reduction of mortality are diphtheria, tetanus, poliomyelitis, smallpox and yellow fever—diseases, that is to say, resulting from the action of a bacterial exotoxin or of infection by a virus. For the transmission of none of these diseases, with the partial exception of poliomyelitis, can a poor standard of hygiene be chiefly blamed. But it is quite otherwise with tuberculosis and the intestinal infections. In protection against these diseases vaccination should never be regarded as more than an adjunct to the radical measures of controlling the source and the means of transmission of infection by strict attention to personal and environmental hygiene in the widest sense. Vaccination, as I hope I have made abundantly clear, is, like chemoprophylaxis, not without its dangers, and should not be used as an excuse for inaction in applying the well-tried standard methods for the prevention of infectious disease.

Mass immunization

Most important is, it to realize the potential dangers of mass immunization. In such an operation time does not permit an inquiry into the suitability of each individual subject for vaccination. An allergic history, such as that of sensitivity to egg protein, horse dander, horse serum, or penicillin; a history of eczema either in the subject to be vaccinated or in a member of the family; a history of asthma from whatever cause; any stage of pregnancy; the presence of certain blood dyscrasias; current treatment with corticosteroids, irradiation or alkylating agents; recent administration of other vaccines and sera; as well as the age, general health and state of nutrition—should all be taken into consideration before a person is inoculated, for example, with smallpox vaccine; but this is not possible under the conditions of mass immunization. The ideal in any country is for the routine immunization of children to be so well organized that mass immunization should seldom, if ever, be called for. This is perhaps a counsel of perfection, but it is the only way in which the dangers unavoidable in mass immunization can be circumvented.

The avoidance of mass immunization presupposes the existence of a thorough programme of immunization during childhood. And here we might well copy the example of our Russian colleagues. In the Soviet Union every child is brought to the clinic once a year up to seven years of age for general examination and for inoculation and reinoculation. The advantages of such a system in enabling a watch to be kept over the physical and mental health of the child during its most crucial developmental years and in ensuring the fullest degree of protection against infectious diseases by a well-thought-out programme of immunization need not be stressed.

In England and Wales, on the other hand, we have still a long way to go. Supervision during the first year of life is undertaken fairly satisfactorily at the Infant Welfare Centres, but after that there is a gap till the time of school entry during which the child receives no routine series

of examinations. When medical officers of health are advised to defer vaccination till the second year of life or to give a reinforcing dose of vaccine at 18 months against some infectious disease they complain that they have great difficulty in getting hold of the children at this age. This is perfectly true; but surely the right answer is to adjust the administrative procedure so as to ensure an annual inspection, with the opportunity of inoculation and reinoculation, of every child during the whole of the pre-school period. Were such a policy carried out effectively, then mass immunization with its attendant dangers should seldom be necessary.

New vaccines

A very difficult problem with which one is faced is the introduction of a new vaccine. It is noteworthy that most of the major accidents that have occurred in the history of applied immunology have concerned new products or new methods of making old products. Some of the risks that may be encountered have been dealt with incidentally in the present survey; but for a description of other risks, such as contamination with foreign viruses—particularly those of the tumour-producing group—reference may be made to the report published by the World Health Organization (Report 1966). Animal experimentation may afford little guidance to the toxicity, infectivity or protective power of a vaccine for human beings. Indeed the reaction of animals to it may be misleading, as in the behaviour of the mouse to Felix's alcoholized typhoid vaccine, or to the intranasal test for the protective activity of pertussis vaccine. Naturally every test that is likely to throw light on the reactivity of the human subject must be carried out on animals; but the final test is the reaction of man himself; and of the outcome of this test it is unwise to predict too closely.

In the first place the vaccine should be tried on a small number of picked subjects, preferably of different ages, who can be kept under continuous supervision for some weeks at least. It must be remembered that some diseases, such as rabies and serum hepatitis in man and scrapie in sheep, may have a very long incubation period; and, if the vaccine is a living one, it is impossible to be sure of its harmlessness until the vaccinated subjects have been kept under observation for a year or more. Should the vaccine appear to be without danger, then a second trial for safety should be carried out on a larger group of subjects in case post-vaccinal complications are too few to be detected on only a small number. Once the safety of the vaccine is reasonably assured, controlled trials should be put in hand to determine the degree of its protective ability. These should be made in different areas of the country, and in different socio-economic groups, because it cannot be assumed that the basal immunity or reactivity of all the groups will be alike. Not until this information is obtained and other factors are taken into account can a balanced judgment be expressed on whether routine immunization of the child population or of selected groups of the population is worth while undertaking.

Apart altogether from the inconvenience to parents and children of adding to the burden of routine immunization, and the adverse effect on the immunization programme in general, that the introduction of a new vaccine may have, it should be remembered that the force of precedent in Great Britain is very strong. As I have pointed out elsewhere (Wilson 1947), it is far easier to introduce a new measure into public health practice than it is to discontinue it once it has become well established.

The consequence is that many practices tend in time to become anachronistic and the reasons why they were originally introduced tend to be forgotten. This holds especially true of immunological practice. The prevalence of different organisms or types of organism, the environmental conditions in which they operate, the natural or acquired resistance of the population, and other factors result in a continual change in the epidemiological milieu. For this reason immunological programmes should be subjected to constant scrutiny lest practices should be perpetuated that are no longer necessary. Not unless the probable benefits greatly outweigh the disadvantages should a new vaccine be introduced for routine use.

Incidentally, experience of the past should teach us how unwise it is ever to introduce a new vaccine without first determining its protective power in man. Once a vaccine has been introduced, with apparently good results, it becomes extremely difficult ever to find out its real value. Moral objections may be too strong to permit a properly controlled trial. So long as there is some reason to believe that the vaccine is of benefit, it is considered unjustifiable to protect only a proportion of the children in a field trial and expose the others to the risk of the disease.

This objection may perhaps be overcome provided there is an effective method of treating the unvaccinated subjects who are unfortunate enough to contract the infection. Vaccination against typhoid fever is to some extent a case in point. From the time of its introduction at the end of last century up to a few years ago there was no exact knowledge of the usefulness of this measure. The disease was accompanied by too high a fatality rate to justify the risk of a properly controlled field trial; and it was not till the specific effect of chloramphenicol in treatment had been recognized that properly conducted field trials of the vaccine became possible. It is true that an extensive and admirable series of observations had been made between 1905 and 1909 on the incidence and death rate of typhoid fever among British troops proceeding abroad (Leishman 1909), but the conditions under which they were made were not such as to satisfy the most critical scrutiny (Cockburn 1955). It required the carefully controlled trials in Yugoslavia and British Guiana to prove the value of this vaccine beyond all doubt (Report 1962*d*, 1964*a, b)*.

With rabies vaccine, on the other hand, the position is different. The vaccine has been used ever since its introduction by Pasteur in 1885; but we still have no exact measure of its protective power because no field trial has ever been carried out. Rabies, when it develops in man, is uniformly fatal. We have no cure for it, so that, even if we believed that rabies vaccine was of no value at all, we could not morally carry out a trial to find out its efficacy or uselessness. We shall have to go on using it until some other method is found of preventing the disease or until we learn how to cure it once it has developed.

In avoiding trouble after vaccination I need hardly draw attention to the need for proper control over the production, transport, storage and use of the various reagents concerned. The numerous accidents that I have recounted in these lectures should be sufficient warning of the dangers attendant on any laxity in these respects. Particular care must be exercised when dealing with new products. Diphtheria toxin-antitoxin mixture and the Salk poliomyelitis vaccines are two cases in point. The dangers of dissociation of a toxin-antitoxin mixture were not fully appreciated when TAM was introduced, nor in fact were they all known. It took the accidents at Concord and Bridge-water to reveal the deleterious effect of freezing on the stability of the mixture. Moreover the need to prepare the

original mixture in such a way as to avoid the operation of the Danysz phenomenon was sometimes overlooked, with the result that free toxin was present in the final product, as probably occurred at Dallas, Texas, in 1919.

Failure to realize fully the limitations on the disinfecting power of formaldehyde in the presence of organic matter, especially its poor penetrability into protein-containing particles, led to the Cutter incident of 1955 with poliomyelitis vaccine. These limitations had been known to bacteriologists for years, but unfortunately this knowledge was not made full use of by the manufacturers of the product.

The Lübeck disaster was far more inexcusable. Here was a matter not of failure to appreciate or apply scientific knowledge, but of sheer stupidity in holding virulent and attenuated cultures in the same incubator. The same lack of common sense was responsible for the Baden catastrophe of 1924 which resulted from keeping flasks of free and of neutralized toxin side by side in the same cold cabinet.

It needed the tragedies of Mulkowal and of Bundaberg to impress on manufacturers the danger of omitting the addition of an antiseptic to vaccines or sera that are likely to be exposed to atmospheric temperature before use. Whether the risk of provocation disease, and even of anaphylaxis, is yet fully recognized is doubtful, but it is one that should always be borne in mind.

Experience in the control of water, milk, ice-cream, and certain food products has shown that, on the average, a much higher quality is attainable by a large firm or undertaking than by a small. Large firms have many advantages. They have more capital by means of which they can provide the best plant and equipment, employ a better-educated staff of managers and foremen, and afford methods of control and inspection that would be far too expensive for the small firm. There is much to be said therefore for limiting licences for the production of immunological products to a few large manufacturers. This has the additional advantage of making it easier to control the quality of the distributed product, and to trace the source and cause of any fault that may arise.

Surveillance

One further point. We want a really effective system of surveillance to detect any accidents that may follow vaccination, as well as to keep a record of the more usual complications. A well-organized system of public health should maintain close watch over all forms of illness occurring in the country, paying particular attention to unusual diseases and to unusual aggregations of cases of disease. Sequelae that do not manifest themselves for weeks or months are likely to be neglected unless they are being looked for.

The task of surveillance must include the long-term effect of vaccination procedures that cannot be determined by the ordinary field trial. BCG vaccination offers an example of our ignorance of its effect on the total prevalence of tuberculosis. That it affords a high degree of protection against the clinical manifestations of primary tuberculosis is well attested; but we have little information on its effect on the incidence of the adult or late-adult types of disease which contribute 98 per cent or so of all deaths from tuberculosis in England and Wales. Nor are we fully cognizant of the potential danger of vaccinating tuberculin-positive subjects. These are matters for a national surveillance scheme. The comparative effect of vaccinating populations having different degrees of

genetic immunity and of personal and environmental hygiene is also worth studying, but is better suited to an international body which can bring several different countries within its purview.

The organization of a surveillance scheme must of course be adapted to the structure of health control in each country. In England and Wales it should be the responsibility of the medical officers of health and the Public Health Laboratory Service under the general supervision of the Ministry of Health. No pure office system is satisfactory. Numerous cases of infective disease and small outbreaks are recognized first in the laboratory; and many of these cannot be adequately investigated without the help of a field epidemiologist, who should preferably be attached to the laboratory. On his side the medical officer of health receives notifications and records that may pose problems demanding inquiry. As part of the surveillance programme medical officers of health should subdivide the population under their care into groups, according to age, sex, pregnancy, occupation, immunization history, and other variables, so as to be able to detect any unusual frequency of disease in the various groups. In this way attention may be drawn to sporadic cases whose significance might otherwise be missed.

Finally, I want to make it abundantly clear that I am not an anti-vaccinationist. This perhaps hardly needs saying, but I do say it because of the ease of misrepresentation. In the United States last year I was referred to in a medical journal with one of the largest circulations in America as an anti-vivisectionist, because I gave evidence before a subcommittee of the Senate on the limitations which the Cruelty to Animals Act imposes on scientific workers in Great Britain, and expressed the opinion that there is a degree of pain which no scientist has the right to inflict on any animal, no matter what increase in knowledge he may hope for from the experiment.

Vaccines, of one sort or another, have conferred immense benefit on mankind but, like aeroplanes and motor-cars, they have their dangers. My intention has been to provide information on these dangers in the belief that, unless they are known and recognized, the task of guarding against them is bound from time to time to meet with unexpected and possibly disastrous failures. Manufacturers entrusted with the preparation of immunological products must, in particular, be careful to maintain eternal vigilance. A single slip may be disastrous.

Over-confidence must at all costs be avoided. St Paul issued a warning against this: 'Let him that thinketh he standeth take heed lest he fall'; and Shakespeare expressed the same thought in even stronger terms:

> And you all know security
> Is mortals' chiefest enemy.

It is for us, and for those who come after us, to see that the sword which vaccines and antisera have put into our hands is never allowed to tarnish through over-confidence, negligence, carelessness, or want of foresight on our part.