

## LABORATORY-ACQUIRED INFECTIONS

S. EDWARD SULKIN<sup>1</sup>

*Department of Microbiology, The University of Texas Southwestern Medical School, Dallas, Texas*

Although numerous individual case reports and a few instances of institutional outbreaks of laboratory-acquired infections had appeared in the literature, the magnitude of this problem as it relates to the occupational health of laboratory workers did not become evident until the results of an extensive survey conducted in 1950 became available. Prior to that time only an occasional report concerned itself with consideration of the need for adequately protecting personnel who come in daily contact with disease-producing agents. By means of a questionnaire circularized to several laboratories in the United States, Meyer and Eddie (26) in 1941 assembled pertinent information regarding laboratory infections due to brucellae. From published reports and personal communications, Sulkin and Pike (34) in 1949 collected data regarding the occurrence of viral infections contracted in laboratories in the United States and elsewhere in the hope that such information would indicate where the greatest need for caution exists in work with viruses. To obtain more information regarding the occurrence of laboratory infections, the National Institutes of Health sponsored a survey which was conducted about 10 years ago. Questionnaires mailed to nearly 5,000 laboratories in the United States revealed over 1,300 instances of presumed laboratory-acquired infection, with 39 deaths (35). Since that time an effort has been made to maintain a file of laboratory-acquired infections as they are reported in the literature and as they are called to our attention. A section on this subject in *Diagnostic Procedures and Reagents*, published by the American Public Health Association, contains a summary of 2,262 cases with 96 deaths (36). Since that manuscript was prepared, 86 additional cases (with 11 deaths) have come to our attention bringing the total to 2,348 cases, with 107 fatalities.

<sup>1</sup> Chairman, Committee on Laboratory Infections and Accidents, American Public Health Association. To further the work of this Committee, investigators are urged to report instances of laboratory infections and accidents to the author of this article.

Since many laboratories do not keep records of instances of laboratory infection, much information was given from memory and some from hearsay only. Furthermore, some commercial laboratories were unable to provide information because of a company policy not to release such data, although a few freely provided the information requested. Also there is little doubt that numerous laboratory-acquired infections of a mild nature have escaped diagnosis entirely. These facts indicate that the number of cases which have come to our attention represents perhaps only a modest fraction of those which have actually occurred. Moreover, an analysis of the data which have become available unfortunately does not provide information concerning the number of organisms required to produce recognizable illness under a variety of circumstances.

A great variety of disease-producing agents is involved representing bacteria, viruses, fungi, rickettsiae, and protozoa. The highest proportion of deaths occurred among those persons infected with viruses with a case fatality rate of 7.3% as compared with 4.0% for bacterial, 2.6% for rickettsial, and 2.3% for fungal infections. No fatalities occurred among the cases of parasitic infections.

The diseases most frequently encountered were brucellosis, tuberculosis, and hepatitis, which together accounted for about one-third of all infections. There are many agents with which relatively few persons have laboratory contact, yet the number of infections caused by them has been large. For example, tularemia, psittacosis, typhus, Q fever, and coccidioidomycosis occur as institutional outbreaks or as scattered cases in laboratories where the organisms producing these diseases are studied intensively.

Laboratory infections are not confined to the personnel most closely associated with the infectious agents. Although professional and technical workers, research assistants, and graduate students experience about three-fourths of the illnesses, office workers, janitors, and dishwashers became infected as a result of activities in the laboratories with which they were associated.

In an attempt to analyze the data which have become available to us, the cases have been classified according to the proved or probable source of the infection. If one removes the known accidents which are preventable in the sense that most accidents can be prevented, it becomes clear that a major proportion of the remaining infections result from aerogenic transmission of the agent. An effort will be made to limit the remaining portion of this discussion to those areas which relate to the subject of this Conference.

The exact source of a laboratory-acquired infection is frequently obscure. Often it is known only that an individual had been working with a particular agent or that he had been in contact with infected animals or ectoparasites. In other situations it is known that the atmosphere of a laboratory had become contaminated with pathogenic organisms. This potential source of infection has been more fully appreciated since workers at Fort Detrick (29, 41) have designed atmospheric sampling devices which show that such common and simple procedures as removing stoppers, pipetting fluids, and flaming inoculating needles may produce aerosols near the laboratory bench. This subject will be discussed more fully by Wedum (42).

In analyzing the data which have become available to us, a category labeled "aerogenic transmission" was reserved for those cases in which this source appeared to be most likely, even though the actual mode of transmission in many of those infections which were listed as having resulted from "work with the agent" may well have been aerogenic. In some instances the evidence for aerogenic transmission was fairly well documented. For example, a fatal case of typhoid fever resulted from opening a lyophilized culture, and two cases of typhus and one of rickettsialpox apparently resulted from the use of the Waring Blendor. In many more instances aerogenic transmission was listed as the probable source of a laboratory-acquired infection although this could not always be clearly established. It may be assumed that most laboratory infections which do not result from poor technique or accidents are generally connected with inhalation of infectious material. Contamination of the air may arise from many sources. One of these is the Waring Blendor, which has come into wide use for the emulsification of infected tissues. Although relatively few laboratory infections are directly

attributable to use of the Waring Blendor, special precautions are indicated.

Tuberculosis, which ranks second among the bacterial diseases, has been a matter of special concern because of the large numbers of persons who handle tuberculous materials in clinical, research, and teaching institutions and because of the severity and prolonged course of the disease. Since the onset is insidious and since there are numerous opportunities to acquire the disease outside the laboratory, it is usually impossible to trace the source to any given incident that might have resulted in infection. Consequently, in most instances, only circumstantial evidence points to the origin of infection in the laboratory. The potential hazard of acquiring tuberculosis is considered to be so great that several medical schools no longer permit classes to study materials containing living tubercle bacilli.

Long (21), reporting 10 years ago on the hazard of acquiring tuberculosis in the laboratory, noted, "Probably the danger of infectious aerosols from bacillary suspensions is now of greater moment than ever, since culture media designed for subsurface growth and maximum dispersion of bacilli favor the presence of organisms in extremely minute droplets, of the size most likely to penetrate to the deepest recesses of the lungs and set up pulmonary infection." This comment is just as pertinent today as it was 10 years ago. Other sources of laboratory-acquired tuberculosis are well recognized and include secretions from infected animals, dust from dried contaminated materials, and aerosols produced by overenergetic discharge of suspensions of tubercle bacilli from hypodermic needles and pipettes.

Evidence of aerogenic spread of tubercle bacilli in animal rooms was presented 30 years ago by Lurie (22). Spontaneous tuberculosis occurred from time to time in presumably normal guinea pigs housed in the same room with tuberculous animals. Infection in these animals was usually by the way of the respiratory tract and the frequency increased with the duration and intensity of exposure. In studies reported later, Wells and Lurie (43) showed that normal rabbits almost invariably become infected if exposure is allowed to continue for several months. Animals were exposed in specially designed chambers to airborne infection from tuberculous rabbits. These observations indicate the dangers to which lab-

oratory workers and animal caretakers may be exposed. Their studies further indicated that proper use of ultraviolet light will sterilize the atmosphere. The foregoing facts, together with the recent studies of Riley and his associates discussed elsewhere in the proceedings of this Conference (30), indicate that emphasis upon measures to prevent contamination of the air would certainly be effective in limiting the occurrence of tuberculous infection among laboratory workers.

It has long been known that the physical proximity of normal animals to animals infected with certain viruses is sufficient to cause infection in the former. This pertains to a number of viruses and may not only present a hazard to those working in the immediate area but also complicate interpretation of laboratory data resulting from the use of such animals. Contact infections have been demonstrated among normal animals which have been in association with those infected with the viruses of poliomyelitis (4, 15, 47), influenza (14, 32), distemper (6, 14), psittacosis (19), and lymphocytic choriomeningitis (37), to mention a few. White mice may harbor the virus of lymphocytic choriomeningitis as an inapparent infection. Infected animals eliminate the agent through nasal secretions, urine, and feces, and aerosols may carry the virus not only to normal animals but to workers and caretakers. Laboratory animals may also serve as a large reservoir of leptospire which are shed in the urine. *Leptospira ballum* is commonly found among laboratory white mice (46) and natural infection with *Leptospira icterohaemorrhagiae* has occurred among white rats and guinea pigs (23, 39). White rats may become inapparent carriers of leptospire as a result of inadequate "wild" rodent control in the normal animal colony. In Europe *Leptospira grippotyphosa* has been isolated from naturally infected hamsters (28) and in the United States a new strain of leptospire, belonging in the *Leptospira hebdomadis* subgroups and designated *Leptospira mini georgia*, has been isolated from naturally infected raccoons, opossums, and a striped skunk (8). A laboratory infection with *L. ballum* was traced by Wolff, Bohlander, and Ruys (44) to the urine of laboratory white mice and recently Stoenner and MacLean (33) reported infection of eight laboratory employees who had close contact with Swiss albino mice which were infected with this organism. Through a labora-

tory accident it was demonstrated that the recently characterized leptospire, *L. mini georgia*, was infective for man (10). At least 16 laboratory-acquired infections with B virus have occurred since this agent was first demonstrated in 1932; 10 of these occurred in 1957 and 1958 probably as a result of increased use of monkey tissues for cultivation in vitro of poliovirus and for safety testing of vaccine. Although many of these infections resulted from monkey bites or handling of these animals, there is the suggestion that some persons might have acquired their infection through aerogenic means.

Precautions that may have to be taken to limit the occurrence of laboratory infections are well illustrated in the case of Q fever, which involved many laboratory workers in the first few years of study of its causative agent. The relatively stable *Coxiella burnetii* is excreted in the urine of infected laboratory animals and the inhalation of dried cage litter may have accounted for one of the institutional epidemics of Q fever (16). In at least one laboratory where this agent has been handled extensively, procedures likely to produce infectious aerosols are avoided. Infected animals are housed in separate quarters. Triethylene glycol aerosols are maintained in work rooms and animal houses to help disinfect the atmosphere, and in addition all personnel are immunized with vaccine. The result has been the virtual elimination of Q fever infections in this laboratory (25).

The opening of sealed glass ampoules which contain lyophilized active viral or rickettsial material constitutes a serious inhalation hazard in the laboratory. Special techniques have been recommended for opening such ampoules. The circumstances leading to a case of psittacosis were carefully reconstructed by Rosebury, Ellingson, and Meiklejohn (31) to show how a leaking ampoule containing a suspension of yolk-sac virus had contaminated the worker's hand and surrounding atmosphere.

The cases of infection among laboratory personnel apparently resulting from the handling of infected chick embryos attest to the potential contagiousness of such material. Chick embryo cultivated virus was thought to be the source of infection in two cases of Western equine encephalomyelitis (9, 12), in four cases of Venezuelan equine encephalomyelitis (18), and in a case of Eastern equine encephalomyelitis (27). Among the cases of psittacosis, of particular interest is a

laboratory worker who had handled infected birds and mice for several years without infection but who became ill with proved psittacosis after working with a suspension of virus from chick membranes (2). Five laboratory infections with the agent of lymphogranuloma venereum occurred among persons working with infected chick embryos (11). It was pointed out that one factor that contributes to the danger in handling infected embryonic egg tissues may be the high concentration of virus in such material (24).

An analysis of the circumstances leading to certain of the laboratory infections has provided important information regarding the transmission of these diseases. For example, since contaminated dust from mouse cages was apparently responsible for several infections with the virus of Venezuelan equine encephalomyelitis, it seemed likely that infection was by the respiratory route (20). The possibility of direct transmission of the equine encephalomyelitis viruses suggested by these observations is of interest since it indicates that under these circumstances the disease may be transmitted to man in the absence of known arthropod vectors. The same may be said for a case of encephalitis which occurred in a person working with the St. Louis encephalitis virus (40).

Those agents which are the chief offenders in causing infections among laboratory personnel are likely to show the greatest possibilities for use in biological warfare. The agents most often involved in laboratory-acquired infections are a matter of record and are generally recognized to be hazardous. One thing that may be overlooked is the fact that laboratory infections do not always follow the pathways of transmission established for the naturally occurring disease. For example, the typhoid bacillus has certainly been considered as a potential agent of biological warfare. Those concerned with the means of defense in biological warfare would probably think first of contaminated food and water supplies in connection with the transmission of typhoid fever. The survey, however, revealed at least one case in which the infection was transmitted aerogenically when a worker opened a tube containing lyophilized culture. Although the actual route of infection in this case was probably by way of the gastrointestinal tract, the incident suggests that an effective degree of atmospheric contamination might be produced

by means of such material. A number of laboratory-acquired cases of brucellosis have occurred among persons exposed only to atmosphere contaminated by brucella organisms. In tularemia there are instances in which there is not only circumstantial evidence for aerogenic transmission but also the pneumonic nature of the infection points to this route. In neither brucellosis nor tularemia is aerogenic infection thought to be important in the natural transmission of the disease.

Laboratory infections due to at least three viruses have evidently been transmitted by unnatural means. Of 17 cases of encephalitis recorded, none was thought to have been transmitted by an arthropod. The means of transmission was largely unknown, but, since many of these cases occurred in persons who worked with the agent, aerogenic transmission is a distinct possibility. There have been 2 cases of encephalitis, however, in which there had been no direct contact with the virus but only brief contact with potentially contaminated atmosphere. Of 14 cases of yellow fever, only 1 was thought to be due to the bite of an infected mosquito. Three individuals had been working with dried virus preparations which would provide ideal circumstances for aerogenic transmission. It is of interest that laboratory-acquired yellow fever was more common before introduction of the lyophile process, when individuals worked with dried infectious tissues often in open containers. Lymphogranuloma venereum, which occurs naturally as a venereal disease, has been responsible for five cases of respiratory infection in laboratory workers who had direct or indirect contact with contaminated materials.

About one-seventh of all laboratory infections which have come to our attention have been caused by rickettsial agents. Of all of the rickettsial diseases, Q fever is the only one naturally transmitted in the absence of an arthropod vector. Of course, the fact that an agent is likely to cause infections in the laboratory does not mean that it fulfills all of the qualifications which have been established for the ideal biological warfare agent. Most laboratory infections represent specialized situations and are usually due to exposure to fairly fresh material.

All of the above-mentioned agents could be prepared in almost unlimited quantities, but there might be difficulty in maintaining the

virulence of such an agent as the virus of yellow fever under conditions of laboratory propagation. On the other hand, it is well known that typhus rickettsiae will survive in dried louse feces for considerable periods of time and the same might be true for preparations of yolk-sac material. These and other examples should be of interest to those concerned with protection against biological warfare because they suggest that even in the absence of some of the links in the usual chain of transmission a given agent might be a potential danger if properly dispersed in the environment.

In several instances a disease was first recognized in man as a result of infection among laboratory personnel. The first human infection with the virus of Aujeszky's disease (pseudorabies) occurred in a laboratory worker (38). Six cases of laboratory-acquired infection with louping-ill virus were the only known human cases until two naturally acquired cases were reported in 1948 (5), and the first infections with the Newcastle disease virus among human beings were laboratory infections involving the eyes (1, 3). The first known human case of Q fever in the United States was a scientist visiting a laboratory where studies with the causative agent, *Coxiella burnetii*, were in progress (7). More than 60 cases of Q fever due to laboratory-propagated strains of this microorganism had occurred in the United States before the disease was found to occur naturally among packing house workers. Soon after *Rickettsia akari*, the cause of rickettsialpox, was isolated in New York City in 1946, four cases of rickettsialpox occurred among laboratory workers. Also shortly after the discovery of the Coxsackie viruses in 1948, when their relationship to human disease was not completely understood, several workers acquired laboratory infections which presented the clinical features later to be ascribed to this group of viruses. A laboratory infection with adenovirus type 8 with resulting typical clinical epidemic keratoconjunctivitis firmly established the etiological relationship of this virus to this clinical syndrome (17). A laboratory infection with ECHO virus (type 9), with resulting aseptic meningitis, occurred after the virus had been through several extra-human passages in monkey kidney tissue cultures (13). Like other members of the Russian spring-summer complex of viruses, the recently described Kayasanur Forest disease

virus has proved to be highly infectious to laboratory workers (45). Clinically apparent infections have occurred in several laboratory workers in India, New York, and Washington. There have been no fatalities. Of special interest is the fact that the benign course of the infection in persons with prior antigenic experience with group B arboviruses (visceral manifestations rather than central nervous system involvement) suggested that this new member of the Russian spring-summer complex may be one of the safer of these viruses to handle in the laboratory even though the infection rate has been high.

Although the significance of the recently isolated bat salivary gland virus in human infection remains to be determined, there is evidence that it may be pathogenic for man, producing systemic illness with complicating orchitis or ovaritis. At least five laboratory-acquired infections have occurred since this virus, related to the St. Louis encephalitis complex of viruses, was isolated in 1956. In these and many of the other instances of laboratory infections cited, it is possible that the infection was acquired by aerogenic means.

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