LABORATORY-ASSOCIATED INFECTIONS: Incidence, Fatalities, Causes, and Prevention

Robert M. Pike

Department of Microbiology, Southwestern Medical School, University of Texas Health Science Center, Dallas, Texas 75235

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INTRODUCTION

For over a century laboratory workers have occasionally become infected by the microorganisms with which they were working, and some of these infections have resulted in death. Because reporting laboratory-associated infections has been largely voluntary, there is no way to arrive at an accurate estimate of the number of persons involved. A survey of the problem, however, indicates that the incidence of such infections increased as new agents were discovered and as more and more workers were involved in handling infectious agents. In recent years increasing attention has been given to safety in the infectious disease laboratory. Attempts have been made to define the extent of the problem, to determine the causes of accidental infection, and to devise safe equipment and procedures. The indications are that these efforts may be having some effect on the incidence of laboratory-associated infections.

INFECTIONS IN GENERAL

Recorded Cases

Many infections of presumed laboratory origin have been reported in the literature, because the author wished to caution other workers of the possi-
LABORATORY-ASSOCIATED INFECTIONS

bility or because the circumstances were dramatic or unusual, and others have been mentioned because the case provided an opportunity to describe the clinical aspects of the disease, although the fact that the infection was laboratory acquired was incidental. On the several occasions authors attempted to learn of incidents by means of questionnaires, numerous cases came to light that otherwise would have remained unrecorded. Such surveys have been made for typhoid fever in Germany (34, 81, 82), for brucellosis in the U.S. (106), and for hepatitis in Great Britain (51, 52). A survey limited to the U.S., but including all types of infectious agents, was conducted by mail in 1950 (177). Replies listed 875 unpublished cases, in addition to 467 published ones. Among these 1342 clinically apparent cases there were 39 deaths. During the next 13 years an additional 641 cases occurring throughout the world were tabulated from publications and from personal communications (136). By continued surveillance and a search of the world literature through 1974, it was possible to list 3921 cases of clinically apparent infections that were classified according to the agent involved and, if known, the source of infection and the type of work in which the victims were engaged (133). In a more recent summary (134) the total had increased to 4079.

Obviously, many infections must have occurred that are not recounted in the data given above. Since only about 60% of the recorded cases have been published (133), there are certainly many others that the limited inquiries have not disclosed. For example, during conversations in 111 laboratories in 18 countries numerous cases of which there were no records were recalled (126). Phillips estimated that approximately 6000 infections had been mentioned in publications (128). If one were to include inapparent infections that became known only if an immunologic response was looked for, our total (134) would be at least that high. The examples of brucellosis (68, 115), tularemia (188), histoplasmosis (46), coccidioidomycosis (170), Newcastle disease (80), Q fever (26, 102), hepatitis (86, 123), and Coxsackie disease (165) suggest that subclinical infection has occurred more often than has infection with recognized symptoms.

INSTITUTIONAL AND COMMON SOURCE OUTBREAKS Some infectious disease laboratories have experienced outbreaks of infection either from a common course or over a relatively short period of time.

Q fever The first outbreak of Q fever was reported in 1939 in Australia (17). It involved only four persons, of whom two had subclinical infection. A larger outbreak occurred at the National Institutes of Health, Washington, D.C., in which 153 employees had the disease over a period of 54 days (35, 67); one of them died. Epidemiologic data suggested that the agent was
dust-borne. Eight years later, at the same institution, 47 persons were infected (69). The preparation of yolk sac antigens from infected eggs was suspected as the source. During World War II the 15th General Medical Laboratory in Naples, Italy, reported 20 cases over a period of 3 months (151), and the laboratory at Fort Bragg, North Carolina, experienced 16 cases in a 6-month period (23). Both of these outbreaks were traced to work with infected chick embryos. A similar source was suspected as the cause of 12 cases in one building in Serbia in less than a year (47). Two laboratories in Germany in 1948 had clusters of cases, one involving 9 persons (113) and the other 23 (79). In the latter, eight persons had no direct contact with Coxiella burnetii; they merely worked in the building where the agent was being handled. Naturally infected sheep were responsible for the 14 cases that occurred in one laboratory in Italy (152) and for the 16 infections, some inapparent, in Wisconsin in 1969 (26).

**Brucellosis** The largest laboratory outbreak of brucellosis on record occurred at Michigan State College in 1938 in which there were 45 clinical cases, with one death, due to *Brucella melitensis*, and a comparable number of subclinical infections (68, 115). None of the persons involved had handled brucella cultures. Although the means by which the organisms were disseminated was not proven, it was obvious the infections were associated with a brucella laboratory in the building.

**Erysipeloid** Six cases of erysipeloid were observed among veterinary students at Kansas State College during 1 month in 1936, and seven more cases occurred during the next 3 years (53). A horse cadaver was the proven source in one instance and was suspected in the others: All of the victims had slight traumatic injuries in the anatomy laboratory or at the autopsy table.

**Psittacosis** Of the 11 cases of psittacosis (one fatality) that occurred at the Hygienic Laboratory of the U.S. Public Health Service in 1930, only two had been exposed to infected birds (98); the others worked in the same building. McCoy (98) considered this to be the first instance of psittacosis to occur as the result of contaminated environment without direct contact with infected birds.

**Histoplasmosis** The potential of *Histoplasma capsulatum* to infect laboratory personnel was shown by 17 out of 26 employees at the Kansas City Mycoses Laboratory who went from negative to positive in histoplasmin skin test over an average of 4.2 months of employment (46). Clinical illness was observed in seven. During a period of a few months, a laboratory in
Sweden where *H. capsulatum* was being studied recorded seven cases of bronchopneumonia diagnosed as histoplasmosis (116). Following a laboratory exercise in Wisconsin in which *H. capsulatum* cultures were transferred and examined, one out of 17 medical technology students developed clinical illness (33). Because of strong skin reactions to histoplasmin in the remaining students, and positive serological reactions in some of them, it seemed possible that all had been infected. A similar experience involving medical students in California resulted in one overt case of histoplasmosis following a laboratory exercise in which live *H. capsulatum* was examined (110). On the basis of skin tests, complement-fixation reactions, and chest films, it was determined that as many as 26 other students in the class may have had mild or inapparent infection.

**Venezuelan equine encephalitis (VEE)** In 1943, eight persons working in an isolation section of the Yellow Fever Research Laboratory in Brazil contracted VEE within 2 weeks (89). The cases occurred following experiments that exposed the operators to dust from mouse boxes. Eight individuals working in one laboratory in Buenos Aires were infected at the same time by the VEE virus under investigation (155). An outbreak that occurred in Russia in 1956 (167) was remarkable not only for the large number of persons involved, but also for the fact that a single preventable accident and improper handling of the situation after the accident were responsible for the infections. Nine ampoules of lyophilized mouse brain infected with VEE virus were broken on a stairway. Although the immediate areas were disinfected, a door leading from the stairway was opened repeatedly, traffic was allowed to continue, the walls of the stairway were not disinfected, and potentially contaminated coats were worn for 2 days after the accident. As a result, 22 persons became ill within 24–28 hr after the accident and 2 more became ill after 4 days.

**Typhus** Within a few weeks in 1941 there were six cases of murine typhus among the personnel of a German laboratory (91). These infections were believed to have occurred by the respiratory route. The same route of infection was responsible for five cases of murine typhus in one laboratory in England and for seven cases in another (187). In both these laboratories the infections occurred shortly after exposure during the intranasal inoculation of mice. All 12 persons had been immunized, a fact that probably accounted for the relatively mild course of the disease.

**Sources of Infection**

In over 80% of laboratory infections no accident can be recognized as the cause (127, 133, 177). The probable source may be apparent in many of
these non-accident cases, but the mode of transmission is frequently speculative. Often the only information available is the fact that the person worked with the agent or in a room or building where the agent was handled. The probable sources of infections as compiled on three occasions appear in Table 1. The percentage of infections attributed to aerosols applies only to those cases that could not be classified in any of the first six categories listed, but it is obvious that an aerosol might have been involved in any of these. As more data accumulated (Table 1), the distribution of cases according to source remained about the same. The somewhat higher percentages for clinical specimens and autopsies in the 1951 data are probably due to the greater proportion of unpublished cases reported from clinical laboratories in response to a questionnaire.

ACCIDENTS The probable laboratory origin of some infections is based on circumstantial evidence, but when an accident occurs there can be little doubt regarding the source of infection. Accidents resulting in infection can happen in numerous ways that can be classified in a few broad categories. Accident distribution among such categories, as calculated from data accumulated over a period of 25 years, is shown in Table 2. Two general types of accidents occur with the needle and syringe—self-inoculation and spray from the needle or syringe when the two are separated by pressure. Phillips (129) found that accidental inoculation accounted for 4% of 3700 laboratory infections, whereas sprays caused 1.2%. Pipetting accidents have also been an important source of infection. Aspiration through pipettes was the most frequent accident among 3700 infections (129), accounting for 4.7% of the total. Most accidents, as viewed in retrospect, could have been prevented if proper precautions had been taken. Since accidents have not

### Table 1 Distribution of laboratory-associated infections according to source

<table>
<thead>
<tr>
<th>Source</th>
<th>1342 (177)a</th>
<th>1983 (136)a</th>
<th>3921 (133)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accident</td>
<td>16.0</td>
<td>18.8</td>
<td>17.9</td>
</tr>
<tr>
<td>Animal or ectoparasite</td>
<td>10.3</td>
<td>11.2</td>
<td>16.8</td>
</tr>
<tr>
<td>Clinical specimen</td>
<td>13.0</td>
<td>9.7</td>
<td>7.3</td>
</tr>
<tr>
<td>Discarded glassware</td>
<td>1.5</td>
<td>1.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Human autopsy</td>
<td>7.3</td>
<td>5.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Intentional infection</td>
<td>—</td>
<td>—</td>
<td>0.5</td>
</tr>
<tr>
<td>Aerosol</td>
<td>12.9</td>
<td>16.4</td>
<td>13.3</td>
</tr>
<tr>
<td>Work with agent</td>
<td>20.4</td>
<td>22.9</td>
<td>21.1</td>
</tr>
<tr>
<td>Other</td>
<td>—</td>
<td>—</td>
<td>0.4</td>
</tr>
<tr>
<td>Unknown or not indicated</td>
<td>18.5</td>
<td>13.4</td>
<td>19.6</td>
</tr>
</tbody>
</table>

aTotal in each case. Parenthesis indicates reference.
Table 2 Infections resulting from various types of accidents

<table>
<thead>
<tr>
<th>Type of accident</th>
<th>Percentage of accidents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>215 (177)a</td>
</tr>
<tr>
<td>Accident involving needle and syringe</td>
<td>26.5</td>
</tr>
<tr>
<td>Spills, sprays, etc</td>
<td>21.4</td>
</tr>
<tr>
<td>Injury with broken glass or other sharp object</td>
<td>16.0</td>
</tr>
<tr>
<td>Aspiration through pipette</td>
<td>15.4</td>
</tr>
<tr>
<td>Bite or scratch of animal or ectoparasite</td>
<td>14.9</td>
</tr>
<tr>
<td>Centrifuge</td>
<td>2.8</td>
</tr>
<tr>
<td>Other</td>
<td>—</td>
</tr>
<tr>
<td>Not indicated</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*Total number of accidents. Parenthesis indicates reference.

been involved in the majority of infections, it is necessary to look for other potential hazards (see Potential Hazards).

**Incidence in Relation to Type of Work**

Among the 1342 cases analyzed in 1951 (177), infections resulted more often from diagnostic work (33.9%) than from any other activity. Working with materials of unknown character and the large numbers of diagnostic procedures were suggested as possible explanations (92). In the larger collection of cases (133) based on a greater proportion of published infections and a smaller proportion of clinical laboratories, diagnostic work accounted for only 17% of the infections, whereas 59% were associated with research. These latter estimates seem to be more representative.

The majority of infections have occurred in trained scientific personnel and technical assistants, but students, dishwashers, animal caretakers, and clerical and maintenance personnel have also been infected with microorganisms handled in the laboratory (128, 177).

**Trends in Occurrence**

A tabulation of recorded laboratory-associated infections that have occurred in each decade since 1925 (133) seemed to indicate a marked decrease in bacterial and rickettsial infections since 1955, but viral infections continued to occur at about the same frequency from 1945 to 1975. As previously pointed out (133), including in the data infections disclosed by questionnaire (57, 177) added infections during certain periods that would not otherwise have come to light. This variable can be eliminated by considering only those cases reported in the literature and charting them according to the date of publication (Figure 1). Again, a downward trend is seen in recent years, which is even more marked when cases of hepatitis are excluded. Several factors may have contributed to this apparent decline.
Published cases of laboratory-associated infection by decade. Total number of cases, ●; excluding hepatitis, ○.

Among them may well be an increased awareness of the hazards involved and the greater application of safety measures and devices.

INFECTIONS OF SPECIAL CONCERN

**Typhoid Fever**

The typhoid bacillus was the first agent to attract sufficient attention as a cause of laboratory infection to result in a survey to determine the frequency of infection. In 1915, Kisskalt published the first of a series of reports from Germany that listed cases of laboratory-acquired typhoid fever (81). Information regarding 50 cases, including 6 deaths, was obtained from numerous colleagues. Fourteen years later, the same author reported the results of a second survey, which disclosed 62 additional cases, with 5 deaths (82). In 1939, Kisskalt, by then the director of the Institute of Hygiene of the University of Munich, initiated a third survey, which was evaluated by Draese (34). This report added 53 more cases of typhoid fever. Still another summary by Schaefer in 1950 (158) listed an additional 10 cases definitely acquired in the laboratory and 37 others possibly laboratory-acquired, about which there was insufficient information to point to the laboratory as a definite source. Schaefer also noted that rickettsiae seemed to be replacing salmonellae as the major cause of laboratory infection.
**Brucellosis**

The next disease to receive special attention as one likely to be acquired by laboratory workers was brucellosis. Meyer & Eddie (106) reviewed the published reports of laboratory-acquired brucellosis, all from European laboratories and all due to *Brucella melitensis*. To determine the extent of brucellosis in U.S. laboratories, they obtained information from 98 laboratories regarding 74 cases traceable to routine work or research between 1922 and 1939 (106). Among those individuals from whom positive blood cultures were obtained, 21 were infected with *B. melitensis*, 12 with *Brucella suis*, and one with *Brucella abortus*. The prolonged and serious illness that occurred in about half the patients emphasized the need for protective measures.

**Tuberculosis**

The risk of acquiring tuberculosis in the laboratory has received attention for many years, but the number of recorded cases of pulmonary tuberculosis probably underestimates the hazard. Undoubtedly, many cases have not been recognized as laboratory acquired because the long interval between infection and the appearance of symptoms makes it difficult to relate the illness to any laboratory event or activity. In addition, most laboratory infections cannot be distinguished from spontaneous pulmonary tuberculosis otherwise acquired (92). Surveys made to determine the incidence of tuberculosis among laboratory workers as compared to the general population, however, strongly suggest that the problem has been much greater than the number of reported cases would indicate. Over a 10-year period, data showed a tuberculosis case rate among technicians in Ontario, Canada, 28 times that for the general population (103). A carefully conducted survey of 345 laboratories in England for the period 1949 to 1953 (141) showed that technicians handling tuberculous material had a threefold higher incidence of tuberculosis than other laboratory workers. A similar situation has been recognized in France (101, 157), where bacterial aerosols were suspected of being prime causes of contamination in laboratories where work with tuberculous material was occurring (18). The relatively high incidence of tuberculosis among medical students has been attributed mainly to the autopsy room (61, 100, 109, 111), but individual cases have not been well identified.

**Viral Infections**

The expanding interest in viruses and the increasing numbers of persons exposed to these agents in the laboratory prompted a review, in 1949, of viral infections contracted in the laboratory (176). The authors tabulated
222 viral infections, most of which had been reported in publications. There were 21 fatalities. Realizing that arboviruses accounted for a large proportion of laboratory viral infections, and that these agents were being employed in studies of basic biological properties of viruses and their host cells, the American Committee on Arthropod-Borne Viruses undertook a survey of laboratory groups working with arboviruses. The results of this survey, published in 1967, together with cases already on record, indicated a total of 428 arbovirus infections with 16 deaths (54, 57).

HEPATITIS Although hepatitis is the most frequently reported laboratory-associated viral infection (133), its incidence is apparently underestimated. In contrast to most laboratory-acquired infections, hepatitis is more likely to occur in persons engaged in work other than microbiology (12, 149, 181, 199). Hinton (65) recognized hepatitis in test tube washers as early as 1920, but the first 10 years especially, an extensive literature has developed on hepatitis as a hazard to medical personnel. Space permits only a few of these publications to be cited. Kuh & Ward (83) were among the first to emphasize the occupational hazard of working with blood and its derivatives when they reported seven cases among workers in a commercial laboratory. The importance of blood as the major source has been reinforced by other reports (149, 179, 199). Two surveys of clinical laboratories in Great Britain from 1970 to 1974 (51, 52) revealed average annual attack rates of hepatitis for all staff members of 111 and 143 per 100,000, with the highest rate among biochemists. In a survey of Danish laboratories (166), the hepatitis infection rate was seven times that of the general population. The high risk of hepatitis among persons associated with hemodialysis has also been demonstrated (149, 199). The availability of serological methods for detecting hepatitis antigen and antibody has further defined the degree of exposure to the virus. Thus, a survey of 426 hospital staff members found that 40% of those working in clinical chemistry and 20.8% of those working in microbiology had antibody to hepatitis B surface antigen (86). Only 19.3% of those with anti-hepatitis B had a history of hepatitis. Similarly, in another report (123) only 14% of hospital personnel with hepatitis antigen or antibody had a history of overt illness. Inapparent infection, therefore, is even more frequent than clinical hepatitis in these populations.

Another group of laboratory workers subject to greater than normal exposure to hepatitis are those in contact with chimpanzees. Hillis (64) reported 11 cases among 21 persons in contact with young chimpanzees. Nine cases were observed among 209 persons who had contact with 202 imported animals (154). Experimental work with infant chimpanzees resulted in eight cases of hepatitis among 28 persons (97). Of the 234 cases
of laboratory-associated hepatitis tabulated in 1975 (133), 33 were believed to have been contracted from chimpanzees.

**Fungal Infections**

Laboratory-acquired blastomycosis was reported in 1903 (36) and sporotrichosis was reported in 1909 (38), but it was not until 1967 that a detailed review of laboratory-acquired mycoses became available. Hanel & Kruse (56) collected 228 cases from the literature, including both clinically apparent and subclinical cases. Coccidioidomycosis, 108 cases, was predominant. *Histoplasma*, which was not reported as a cause of laboratory infection until 1952 (46), accounted for 81 cases.

**FATAL CASES**

At least 173 persons have died from infection resulting from laboratory accidents or from infection contracted during the course of laboratory-associated activity. The names of some of these workers are well known and some were mentioned by Hunter (71) in his tribute to martyrs of science. Others have been recorded anonymously in the literature. All major categories of infectious agents have been responsible for fatalities.

**Bacterial Infections**

**TYPHOID** The typhoid bacillus has not only caused more laboratory infections than any other bacterium except the brucella group (133), but it has also caused more fatalities than any other agent. Of the 20 typhoid deaths 15 occurred in Germany (34, 74, 81, 82, 158), 1 was reported in France (1), and 4 occurred in the U.S. (177). All of these fatalities occurred before 1950.

**LEPTOSPIROSIS** One half of the bacterial fatalities were due to agents normally transmitted from animals to man (133). Among these, leptospirosis accounted for the greatest number and all occurred in Germany before 1937. One was a laboratory porter who worked in infected animal quarters (14). Four fatal cases were reported among the laboratory personnel working with rat tumors at the Robert Koch Institute in Berlin (159). Among five other cases (196), four were attributable to accidents: Two were bitten by rats, one sustained a needle prick, and another resulted from infected tissue in the eye; the fifth person had handled rats.

**GLANDERS** The nine fatal glanders infections occurred between 1905 and 1925. An accident involving a centrifuge infected four people, three of
whom died (71). Of the four glanders infections mentioned by von Brunn (190), one worked with cultures, whereas three were injured with broken culture tubes. A fatal infection in Prague was associated with the inoculation of a guinea pig with material from a horse with glanders (72). The only known U.S. fatality occurred in 1914, apparently as a result of smoking while autopsying an infected guinea pig [anonymous1 response to questionnaire (177)].

PLAGUE The seven fatal cases of plague have been distributed over six decades. In 1898 an animal caretaker in Vienna contracted fatal pneumonic plague after handling guinea pigs that had cutaneous lesions (105). He then fatally infected his physician and a nurse. Other plague fatalities include an Austrian physician in 1903 (72), T. C. Parkinson at the Lister Institute in 1909 (71), a laboratory worker in Johannesburg, South Africa (90), and Geoffry Bacon, who had worked with plague bacilli for 12 years (31). The last two had received vaccine many times.

ANTHRAX The first fatal case of laboratory-acquired anthrax known occurred in Russia in 1913 (138). The infection was transmitted by the respiratory route while vaccine was being prepared for immunizing horses for the production of immune serum. Smoking while he experimented with anthrax bacilli was thought to be responsible for the death of a young German physician in 1921 (94), although he had been warned that the practice was hazardous. Three fatal cases of anthrax occurred in U.S. laboratory workers in 1941, 1951, and 1958 (anonymous personal communication).

BRUCELLOSIS Allan Macfadyen, Director of the Lister Institute of Preventive Medicine and a pioneer in the study of the effects of low temperature on bacteria, died in 1907. It is not clear whether his death was due to accidental infection with brucella (3, 32, 117) or to laboratory-acquired typhoid fever superimposed on chronic laboratory-acquired brucellosis (81, 153). The following year, T. Carbone, who had been working with Malta fever in Italy for five years, became fatally infected (106). The other three known fatal cases of laboratory-acquired brucellosis occurred in the U.S. One was a student involved in the previously mentioned Brucella melitensis outbreak at Michigan State College (68, 115), one was a technician in a small clinical laboratory in 1938 (W. E. Gemmil, personal communication), and the third was a technician who apparently ingested a heavy suspension of Brucella suis (104).

1Some infections were reported on the understanding that the person and source of information would remain anonymous.
STREPTOCOCCAL INFECTION  Perhaps the first fatal infection that could be considered laboratory associated was that of Kolletscha in 1849 (198). This Vienna physician, an associate of Semmelweis, became severely ill after cutting his hand while performing an autopsy on a woman who had died of puerperal sepsis. In retrospect, it seems highly probable that Kolletscha died of streptococcal septicemia. In 1933, a health department worker in California died of hemolytic streptococcal endocarditis, apparently contracted by tasting raw milk samples during laboratory investigation of an outbreak of streptococcal sore throat (E. L. Russell, personal communication). In Alberta, Canada, a streptococcal infection acquired while performing an autopsy proved fatal to a physician in 1931 (R. M. Shaw, personal communication). A dishwasher in a hospital laboratory in Pennsylvania who died of streptococcal septicemia in 1940 was thought to have become infected from contaminated test tubes (177).

TUBERCULOSIS  In France, in 1938, a man injected himself intravenously with a large dose of tubercle bacilli (88). He developed a pulmonary lesion and splenic enlargement and died after 3 months with terminal meningitis. Before 1950, three laboratory workers in the U.S. died of tuberculosis thought to have been acquired from the cultures or specimens they handled (177).

CHOLERA  One of the earliest fatal laboratory-associated infections was that of Otto Obermeier, who is best known for his discovery of the relapsing fever spirochete (160). He was apparently infected in 1873 by the excreta of cholera patients or by material from patients dead of cholera, which he carelessly kept for study in his bedroom (180). Probably the first fatal laboratory infection reported as such was another case of cholera, which occurred in 1894 when a 29-year-old male research assistant swallowed live cholera vibrios while pipetting (142). Kisskalt (82) referred to two additional fatal cases of cholera. One was a 50-year-old female laboratory assistant who accidentally contaminated her fingers with a pure culture. The other was this person’s roommate, who washed her linen.

MENINGITIS  In 1918, F. N. Torborg, who was engaged in the manufacture of antimeningococcal serum at the State Serum Institute at Copenhagen, died of meningococcal meningitis (71). In the U.S., Anna Pabst, at the National Institutes of Health, was injecting Neisseria meningitidis into an animal when the animal struggled and material from the syringe sprayed into her eye (7). She became ill 4 days later and died after 4 more days.

TULAREMIA  A laboratory assistant at the Rocky Mountain Laboratory of the U.S. Public Health Service died in 1931 of tularemia thought to have
been laboratory acquired (C. Larsen, personal communication). In 1944, a technician at the National Institutes of Health contracted fatal tularemia (6). Although she had not worked with tularemic animals or handled cultures of *Francisella tularensis*, tularemia was under investigation in the laboratory. The early pulmonary involvement strongly suggested an aerosol as the source of infection.

**Relapsing Fever** John Everett Dutton, who studied and named *Trypanosoma gambiense* (37), also studied tick-borne relapsing fever in the Congo. In 1905, during the course of his investigation, he became fatally infected with the organism that bears his name, *Borrelia duttonii* (162). A medical student, collecting ticks in Texas in 1933, contracted fatal relapsing fever (J. L. Terrell, personal communication).

**Other Bacterial Infections** A Peruvian medical student, D. A. Carrion, wanted to study the incubation period and other features of verruga. In 1885, he persuaded a fellow student to inoculate him with blood from a verruga patient (107). As his symptoms progressed, Carrion realized that he was developing Oroya fever. His death demonstrated that the agents of verruga and Oroya fever are the same. A fatal case of dysentery, probably acquired in the laboratory, was reported to Kisskalt (82). In 1935, a graduate student in Minnesota accidentally pricked her finger while injecting a rabbit with a pure culture of staphylococcus. She died of staphylococcal septicemia 3 days later (H. Downing, personal communication).

**Viral Infections**

**Ascending Myelitis** B virus has caused more deaths among laboratory workers than any other virus and it is second only to the typhoid bacillus in fatalities due to all agents (133). This infection also has the highest case fatality rate, 71%, and those who have survived the disease are likely to be incapacitated for months (15, 29, 40). The designation, B virus, derives from the name of the first victim of the disease, W. Brebner, who was bitten by a rhesus monkey in 1932 and from whose brain Sabin & Wright (156) isolated the virus. Of the 15 fatalities 9 occurred in 1957 and 1958 (29, 70, 112, 124, 132).

**Yellow Fever** In 1873, a physiologist in Paris died of yellow fever, which he contracted while examining black vomitus from a yellow fever patient (19). He was apparently aware of the potential hazard because he thought the low temperature of the room where he worked would provide safety. One of the most often mentioned victims of the disease was J. W. Lazear, a member of the Walter Reed Commission sent to Cuba to study
yellow fever in 1900. It has been stated that Lazear's infection resulted from the accidental bite of an infected mosquito (2), but one author (185) was of the opinion that Lazear intentionally placed the mosquito on his arm.

Six of the nine fatal cases of yellow fever occurred between 1927 and 1930. These include Sir Adrian Stokes (118), W. A. Young (119), and Hideyo Noguchi (42), all of whom died in West Africa. The exact circumstances under which they became infected are not known, although Young may have been infected during the autopsy on Noguchi (119). Three others who died during this brief period were an investigator in Brazil who handled blood from an infected monkey (11, 16), an entomologist bitten by an infective mosquito in Nigeria (11), and a technician in London who performed a blood count on a yellow fever patient (73, 93). The most recent case was the young professor, Cuervo, who in 1942 contracted the disease while preparing yellow fever vaccine in Colombia (66).

**MARBURG DISEASE** A previously unknown simian virus caused seven deaths within a period of a few weeks in Germany in 1967 (171). Five persons in Marburg (96) and two in Frankfurt (175) acquired the infection from contact with the blood or tissues of Vervet monkeys imported from Uganda.

**LYMPHOCYTIC CHORIOMENINGITIS (LCM)** Two fatal cases of LCM occurred in persons engaged in the manufacture of distemper vaccine, and a third person who assisted at the autopsy of one of these also died of LCM (5). Smadel et al reported two more fatal cases (169); in one the infection was apparently acquired during an autopsy, whereas the other laboratory worker had no known contact with the virus.

**POLIOMYELITIS** The only published fatal case of laboratory-acquired poliomyelitis was that of a male technician who had been assisting in the feeding of recent isolates of poliovirus to infant monkeys (197). The authors could not speculate as to the mode of infection, but they considered the possibility that infection may have been associated with a recent skin injury. The patient died 2 days after admission to the hospital. A second fatality occurred in Rhodesia in 1946 (J. H. S. Gear, personal communication). The victim had been working with specimens from polio patients for a month prior to his illness.

**ENCEPHALITIS** The first report of a case of Russian spring-summer encephalitis outside of Russia was that of a laboratory assistant in New York who died of the disease in 1953 (75). He had not worked directly with the
virus but had fed and handled animals infected with the virus. A male technician at the University of Pittsburg in Pennsylvania also acquired fatal Russian spring-summer encephalitis as the result of an accident that produced an infectious aerosol (59).

Two of the five known cases of laboratory-acquired Western equine encephalitis (WEE) resulted in death in 1939. One followed a centrifuge accident in which a concentrated chick embryo virus preparation was splashed over two persons in the room (63). One of them, wearing a mask and goggles, was not infected, but the other became ill 14 days later. In another laboratory, a female technician who worked with WEE virus contracted fatal encephalitis (45).

In contrast to WEE, the VEE virus has often infected laboratory workers (133), but it has caused only one death (57); that occurred in one of three persons infected by an aerosol in Bogota, Colombia, in 1955.

A woman who developed a typical herpes lesion in one nostril after harvesting eggs inoculated with herpes virus died of encephalitis (126).

**HEMORRHAGIC FEVER** The Machupo virus has been responsible for one laboratory death in the U.S. (57) and one in Panama (anonymous personal communication). In Argentina, a laboratory infection with Junin virus was also fatal (57).

**LASSA FEVER** The virus of Lassa fever appears to be one of the most hazardous viruses in the laboratory, proving fatal in two out of three laboratory-acquired infections. In 1970, Jeanette Troup became infected during an autopsy on a Lassa fever victim in Nigeria (184). When the newly discovered virus was brought to the U.S. for study, a female laboratory technician in New Haven, Connecticut, working with the virus was fatally infected (85). Another worker in the same laboratory suffered a severe infection (87) but recovered with the aid of convalescent serum after 30 days in the hospital.

**OTHER VIRAL INFECTIONS** A technician who had been working with influenza virus died of influenza (126). The first case of Rift Valley fever in the Western hemisphere was laboratory acquired and fatal (161). A dishwasher in St. Louis, Missouri, was believed to have contracted infectious hepatitis from contact with feces or urine and died of the disease (177). Two technicians died of hepatitis in Canada between 1964 and 1973 (12). In 1972 a microbiologist in Temple, Texas, died of rabies (200). Two weeks prior to the onset of illness he had homogenized infected goat brains by a procedure known to produce aerosols.
**Rickettsial Infections**

**ROCKY MOUNTAIN SPOTTED FEVER (RMSF)** One of the most lethal infections associated with laboratory work is RMSF. All but three of the 13 fatalities occurred in the U.S. T. B. McLintic, A. H. McCray, W. E. Goettinger, and G. H. Cowan, studying the disease in Montana, acquired fatal infections (25, 139) before a vaccine was introduced in 1925 (173), and A. L. Kerlee, who had been vaccinated, died there in 1938 (25, 139). Parker (121) referred to 100% mortality among eight nonvaccinated laboratory workers in Montana, but he did not identify them. The list of RMSF fatalities also includes Lemos Monteira (114) and his assistant, Edison Dias (183), in Brazil, and Breinl, Director of the Institute of Hygiene in Prague (34). All of the above died before 1940. Subsequently, no fatalities were recorded until 1977 when a laboratory helper and a custodian in Atlanta, Georgia, who had not been immunized, died of RMSF (60). Their infections appeared to be related to their employment.

**SCRUB TYPHUS** The first fatal case of laboratory-acquired scrub typhus was reported in Japan in 1931 (120). A technician was infected by the slip of a needle while inoculating a rabbit. About the same time another accident with a needle and syringe, or possibly the same accident, resulted in the death of a research assistant (78). Phillip (125) memorialized five persons, Dora Lush, P. L. Jones, R. G. Henderson, D. J. Hein, and J. E. Roberts, who died of scrub typhus during World War II. The first four became infected as a result of laboratory accidents, whereas Roberts had performed a necropsy on a scrub typhus patient. An additional fatality (186) may have resulted from a respiratory infection acquired while working with yolk sac material.

**EPIDEMIC TYPHUS** Two of the persons who lost their lives while studying epidemic typhus are commemorated in the name *Rickettsia prowazeki*. H. T. Ricketts was apparently infected when one of the lice he collected from typhus patients in Mexico in 1910 escaped from an envelope in his pocket on the way to the laboratory (25). Studying typhus in Serbia, S. J. M. von Prowazek died in 1915 (28). A. W. Bacot, an Englishman working on typhus in Egypt, acquired a fatal infection in 1922 (49), probably from infected louse excreta.

**Q FEVER** The only recorded fatal case of laboratory-associated Q fever was one of 15 persons infected in the outbreak at the National Institutes of Health in 1940 (67).
Fungal Infections
Although a large number of non-fatal cases of laboratory-acquired coccidioidomycosis have occurred (133), the first recorded case was not only fatal (95) but was originally diagnosed as blastomycosis (108). In view of the well-known tendency of arthrospores from cultures of the fungus to cause infection on being inhaled by laboratory workers (170), it is noteworthy that the first infection resulted from a finger prick while performing an autopsy. The second fatal coccidioides infection occurred in a dishwasher at Duke University in 1946. He was one of three individuals working in the same room who were apparently infected by inhaling arthrospores from contaminated flasks (172). The other two had subclinical infections.

A veterinarian engaged in diagnostic laboratory died of blastomycosis (140). The infection was believed to be laboratory associated, but the source was not stated.

In Venezuela, a mycologist acquired histoplasmosis either while working with soil samples or while visiting caves or chicken coops (58). He died 51 days after the onset of symptoms.

Chlamydial Infections
Although the agents of trachoma and lymphogranuloma venereum have infected laboratory workers (133), Chlamydia psittaci is the only member of this group that has caused fatal infections. Only one of the 10 fatal cases of psittacosis occurred since 1949, a fact possibly related to the effectiveness of antibiotics. In 1928, in France, five cases of psittacosis with one death occurred in one laboratory after attempts were made to isolate the agent from a budgeregard thought to be the cause of an outbreak of psittacosis in a household (P. Levine, personal communication). The first of 11 persons infected at the Hygienic Laboratory in 1930 died (98). Three deaths occurred in Germany in 1934 among persons working with the psittacosis agent (43, 44). Other fatal cases have occurred in France (P. Levine, personal communication), England (34), Argentina (K. F. Meyer, personal communication), and the U.S. (150, 178).

Parasitic Infections
The death of Pirie in 1907 was due to visceral leishmaniasis contracted in the Sudan where he was studying kala azar (163). Strictly speaking, the infection may not have been laboratory acquired.

A technician at the University of Tennessee who had worked extensively with Toxoplasma gondii acquired toxoplasmosis and died of the disease in 1951 after a short illness (164). This was the first case of laboratory-acquired toxoplasmosis reported in the U.S.
LABORATORY-ASSOCIATED INFECTIONS

PREVENTION OF LABORATORY-ASSOCIATED INFECTION

Assessment of Risk

Many variables make it virtually impossible to define in precise terms the risk of infection to laboratory personnel handling infectious material. Perhaps the best indicator of risk would be the number of infections that have occurred with various agents in proportion to the number of man hours of exposure. The approximate numbers of known overt infections have been recorded (133), but these figures do not include the many subclinical infections, which, in most instances, are impossible even to estimate and may well out-number those that are clinically apparent. A reliable denominator, man-hours of exposure, is also difficult to obtain. Nevertheless, the number of infections per million man hours has been estimated for selected groups of laboratories and range from 0.1 for clinical laboratories to 50.0 for one European laboratory (129).

Experience has shown that in work with certain agents the risk of infection is extraordinarily high. Thus, in a laboratory where Coccidioides was handled extensively each new member of the team, unless already immune, became infected (170). In another laboratory where Histoplasma was of major concern, the conversion rate for histoplasmin sensitivity among employees was 13.23 per 100 susceptible person months as compared to 0.47 among school children in the same city (46).

A useful approach to the assessment of risk as a working guide for laboratories was devised by Wedum & Kruse (195). In addition to the number of laboratory infections recorded for various agents, they considered the minimal human infectious dose, which has been determined for some disease agents, the recovery of microorganisms from the urine and feces of infected animals, and the frequency of cage-mate infection. Such factors, together with a recognition of the routine techniques that can produce potentially infectious aerosols (10, 147, 148, 174, 193), can provide a useful guide to the hazards involved in working with certain agents. Etiologic agents have been classified on the basis of hazard with recommendations for the conditions under which each class should be handled (20). Oncogenic viruses have been designated as either moderate or low risk, as employed in cancer research (194).

Potential Hazards

Many potential hazards are revealed in a review of the known sources recorded for laboratory-associated infections (see Sources of Infection). The most frequent cause is probably the inhalation of an infectious aerosol (129,
Aerosols may be produced as the result of an accident such as a spill, or they may be produced unintentionally by many microbiological techniques (192). Photography (76) and air sampling (4, 55, 130, 146, 147, 193) have shown that removing the lid from a Waring Blender, removing the closure of a shaken culture, plunging a loop into a flame, and numerous other procedures may release microorganisms into the environment. Lyophilization, animal inoculation, and egg inoculation and harvesting have also been shown to produce aerosols (143–145). It is little wonder, then, that infections have occurred in persons who were known only to have worked with the agent involved. Contaminated animal cage litter, particularly if it is disturbed, can contaminate the environment (50, 168). Numerous infections have been transmitted by the respiratory route in the laboratory, although this may not be the mode of transmission under natural conditions (48, 84, 89, 167, 201).

The needle and syringe, which are involved in about one fourth of all accidents, have been called probably the most dangerous instrument in cancer research (194). This statement might apply as well in other fields of investigation. Many of these accidents could have been avoided if Luer-Lok syringes had been used and if proper care had been taken to secure the animal to be inoculated to avoid unexpected movements (135).

Accidents associated with mouth pipetting, frequent causes of infection in the past (133, 134), are clearly preventable. Pipetting devices to suit almost all situations are readily available (137, 191). Some laboratories prohibit mouth pipetting of potentially infectious or toxic material (21), whereas others prohibit the practice entirely (189).

The potential hazards in various aspects of cancer research were discussed in detail at a conference held in 1973 (62). The precautions indicated for virus research in general were reviewed, and recommendations were made for the assessment and control of any special risk that may be involved in work with tumor viruses. Widespread concern over the potentially disastrous consequences of unlimited research involving recombinant DNA, expressed when this work was initiated, has been replaced by a more rational evaluation of the possible hazards (30).

Protective Barriers

Primary Barriers The clarification of many of the potential sources of laboratory-associated infection has led to the development of protective barriers. Foremost among these are the biological safety cabinets (22, 193, 194) designed to provide protection at the source of potential contamination. In one type of cabinet, air flows into the cabinet away from the operator and is then exhausted through an incinerator or filter. Although containment is not absolute (8, 22), such cabinets, if properly used, should
go a long way toward protecting not only the person working with the agent, but also others working in the room or building who may be infected by the dispersal of an infectious aerosol.

An important advance in containment was the introduction of laminar airflow combined with high efficiency particulate air (HEPA) filters. Laminar airflow, first applied in industry, is widely used in medicine and microbiology (131). Biological safety cabinets with vertical laminar flow of HEPA-filtered air protect both the product and the worker (24, 39, 99) and are recommended for work where absolute containment is not necessary (9, 135, 194). In situations where absolute containment is required, closed cabinets maintaining negative air pressure and providing for work to be performed through ports with attached rubber gloves are indicated (9, 22).

When the possibility of transmitting infectious agents from experimental animals to man or from animal to animal exists, containment is more difficult to achieve. The systems available include cages with filter tops, laminar air flow around cages, and germ-free isolators for the most hazardous agents (50, 194).

SECONDARY BARRIERS In addition to measures to reduce contamination at the source, there are secondary means of providing containment of the more hazardous agents. Laboratory design, limitation of access, control of room airflow with HEPA filtration of exhaust air, and special clothing provide additional safeguards when they are required (9, 194). If vaccines are available, persons at risk should be actively immunized (21).

Responsibility

It has been emphasized repeatedly that measures and equipment designed to prevent laboratory-associated infection are effective only if rules are followed and equipment is properly used. Administrators and laboratory personnel share this responsibility (9, 21, 135, 194). It is the obligation of administrators and supervisory personnel to provide safety equipment and rules governing safe practices (13, 22, 27, 182). Safety manuals (21, 189) are provided by many of the larger laboratories. The effectiveness of all safety measures, however, depends finally on the willingness of the individual to take the necessary precautions and to make a conscientious effort to avoid accidents.

CONCLUDING REMARKS

In the space available it has not been possible to summarize adequately publications dealing with all aspects of laboratory-associated infection. Consequently, some phases of the subject that previously have not been
extensively reviewed have been considered in some detail, whereas brief reference has been made to some problems and solutions that frequently have been discussed elsewhere. It appears that the knowledge, the techniques, and the equipment necessary to prevent most laboratory infections are available and that diligence in the application of preventive measures is necessary if a substantial decrease in the incidence of such infections is to be maintained.

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