

HISTORY & EPIDEMIOLOGY OF LABORATORY-ACQUIRED INFECTIONS (IN RELATION TO THE CANCER RESEARCH PROGRAM)

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I. HISTORY

In reviewing the history of laboratory-acquired infections, it is helpful to determine when the first exposures to laboratory infection began. Some orientation can be gained from Table 1.

As a general rule, the isolation and identification of an agent that causes a transmissible human disease is followed by a laboratory-acquired infection. No less than 120 different microorganisms have caused more than 3,500 lab infections and 160 deaths.

Among the tables provided to you by the late Dr. Sulkin, Table 10 is especially significant in this regard. He has listed 20 diseases in which the first recognition that the agents would infect man was provided by laboratory-acquired infections. This tells you why you have been asked to come to this short course. None of us want this to happen in the cancer research program.

TABLE 1
First Laboratory Infections (Kisskalt, 1915; Riesman, 1898; Birt, 1899)

1676	Leeuwenhoek saw bacteria
1857	Pasteur's paper on lactic fermentation
1866	Koch, first purposive pure culture
1881-84	Isolation & culture of diphtheria bacilli
1898	Diphtheria lab infection by pipette
1882	Koch isolated tubercle bacilli
1882	Glanders
1898	Lab case, syringe
1883	Koch isolated cholera vibrio
1894	Cholera lab infection by pipette
1884	Gaffky isolated typhoid bacilli
1885	Typhoid lab infection, unknown mode
1887	Bruce isolated Brucella melitensis
1897	Brucella lab infection by syringe
1889	Kitasato isolated tetanus bacillus
1893	Tetanus lab infection by syringe

Historically speaking, epidemiological review of laboratory infections had a slow start. Thirty years passed after the first case of typhoid in a laboratory worker before the first survey was made of laboratory infections. In 1915 Kisskalt (Kisskalt, 1915) sent a questionnaire to

“numerous colleagues” in Europe and thereby collected information on 50 cases of laboratory-acquired typhoid fever dating back to 1885. There were 6 deaths. The mode of infection was known in 23 cases, and in 16 of these, the pipette was the cause. In 1929 he reviewed 59 more typhoid lab cases and 24 due to other infectious agents. In these and subsequent reviews (Draese, 1937-1939) in Germany that included several laboratory-acquired diseases, ingestion through a pipette was the most common means of infection. The syringe was next, by spray or injection.

Although the use of mechanical pipettors to prevent possible laboratory-acquired disease is new to the cancer program, it is an old subject in microbiology. The use of mechanical pipettors to prevent laboratory infection appeared in the German scientific journals as early as 1907 (Reinhardt, 1918). There were three of these publications in 1908 (Reinhardt, 1918). In 1918 an Austrian physician (Reinhardt, 1918) described 21 different pipetting devices. He stated “with the aid of the devices described, it is possible to work more quickly than with the oral pipette.”

In more modern times there are reports of laboratory infections by means of the pipette with quite a variety of microorganisms (Sulkin, 1963). In the intestinal group: typhoid, shigella, salmonella, cholera; among others, anthrax, brucella, diphtheria, hemophilus influenzae, leptothrix, meningococcus, streptococcus, syphilis, tularemia; among viruses, mumps (Sulkin, 1963; Enders, 1945), Coxsackie virus (Shaw, 1950), viral hepatitis (Kuh, 1950), Venezuelan equine encephalitis (Ft. Detrick Case, 1958), chikungunya (Shah, 1965), and scrubtyphus (Van den Ende, 1946).

Whether Kisskalt's 1915 survey was responsible I do not know, but the earliest record of use of a protective microbiological cabinet is in Germany, reported in 1919 (Fricke, 1919). In the United States, these protective cabinets for microbiologists did not come into use until the 1940s, when they began to be used at NIH, NBL, and Fort Detrick. In regard to precautionary animal caging, it is reported that in about 1921 a ventilated animal cage rack was put in use at the Paul Ehrlich Institute in Frankfurt, Germany (Phillips, 1961).

In 1940 Horsfall and Bauer at the Rockefeller Foundation apparently were the first in the United States to construct and prove the worth of individual ventilated, air-filtered, compartments in each of which a cage was placed. These Horsfall-Bauer units prevented cross-infections between ferrets inoculated with distemper virus or influenza virus. Control animals remained healthy. However, careful measures were taken to prevent transfer of infectious material by the animal caretaker. He wore a gauze mask, and rubber boots, apron, and gloves that were sprayed at intervals with creosol and the gloved hands dipped in creosol before going from one cage to another. This technique of 30 years ago is now usually omitted, and not enough attention is paid to the fact that anyone handling experimental animals can be the means whereby infection is transferred from one animal to another.

An earlier development that emphasized the careful technique necessary to prevent cross-infection was the work by Reyniers on the rearing of germ-free animals. He began by using a system of glass Bell jars and metal cages during 1928-1932. Then in the 1930s he constructed the metal chambers and cabinets with attached gloves, which he first described in 1943. In a

1946 publication (Reyniers, 1946), he mentions that, as early as 1914, E. Kuster in Germany was using equipment later modified by Glimstedt consisting of "a box lined with metal to which the gloves and a device for transferring food into the cage are attached."

Worldwide interest in laboratory infections began to develop in the 1950s. The Germans started it with their surveys of laboratory-acquired typhoid fever and other diseases, published in 1915, 1929 and 1939. When the USPHS and others began working with psittacosis and Q fever these studies caused multiple infections throughout the laboratory building. From NIH in 1930, McCoy (McCoy, 1930) reported on 11 cases of psittacosis (1 death), which occurred within 60 days. In 1940, Hornibrook and Nelson (Hornibrook, 1940) made an epidemiological study of 15 laboratory infections of Q fever (1 death) at NIH, all within 51 days. In 1947 there was another outbreak infecting 47 persons in 5½ months, reported by Huebner (Huebner, 1947). Q fever rickettsia are unusually resistant, even more than the psittacosis agent. The organisms are excreted in large numbers by infected animals, and are easily disseminated as infectious aerosols during the process of culture in the chick yolk sac, grinding, and centrifugation.

During the 1930s and especially in the 1940s there were many reports of multiple cases of laboratory-acquired typhus. Almost everyone acquired the disease, despite vaccination, during production of the vaccine made by grinding laboratory-infected lice. This situation improved somewhat after Cox in 1938-40 showed that a vaccine could be produced from infected chick yolk sac membranes. Nevertheless, multiple infections continued, from aerosols created during intranasal inoculation of mice, and in other odd situations such as 7 women in a glassware-washing unit in which the autoclaves were not operating properly, and in 3 unvaccinated painters who repainted a typhus vaccine production unit after it was shut down and scrubbed with disinfectant. From NIH in 1944 Dr. Norman Topping reported 17 cases, 9 in vaccinated and 8 in non-vaccinated personnel that occurred in the absence of known accidental exposure (Topping, 1944).

Epidemiological study of laboratory cases at NIH and elsewhere provided valuable information about the relative effectiveness of various laboratory precautionary practices and about building design.

From these outbreaks it was evident there was need to control the movement of air in the laboratory and animal rooms. So, now we have biological safety cabinets, ventilated cages, sealed windows, and negative air balances that move air from the corridor into the room and out in carefully located exhaust ducts. All McCoy had were rooms in which the animals were kept behind moist air curtains, with troughs of disinfectant at the doorways.

McCoy made two important epidemiological observations in his report. These were that there were no infections among employees in nearby buildings, and no infection among members of families of employees. A similar restriction of infection to persons who worked or visited the laboratory building also was reported in two Q fever laboratory outbreaks (20 cases, 47 cases) at NIH (Hornibrook, 1940; Huebner, 1947); in two outbreaks of Q fever at Army laboratories (16 cases in five months at one and 14 cases in another) (Commission on Acute

Respiratory Diseases, 1946); during 10 cases of lymphocytic choriomeningitis at NIH in 1966 (Baum, 1966); and during the course of multiple laboratory infections with other agents such as hemorrhagic fever virus (Kulagin, 1962), histoplasma capsulatum (Hanel, 1967), coccidioides immitis (Hanel, 1967), and typhus rickettsia (Topping, 1944). These infections occurred in the absence of protective ventilated cabinets and filtration of exhaust air. My conclusion (Reitman, 1966), in which others agree (Chatigny, 1961; Barkley, 1973) is that, when appropriate precautionary equipment is provided at the work bench and in the animal room, terminal filtration or incineration of exhaust air from the usual microbiological diagnostic or research laboratory or animal building has no experimental or epidemiological justification. Exceptions would be those laboratories studying dry micronized microbial particles or experimentally created infectious microbial aerosols, pilot plants growing pathogenic microorganisms in aerated tanks with agitators, facilities housing animals inoculated or infected with highly contagious animal diseases, and laboratories utilizing gas-tight Class III cabinetry.

McCoy's other observation, on the absence of infection in the families of laboratory employees, also has been confirmed, subject to the proviso that precautions appropriate for the disease agent should be taken with laboratory clothing. There are reports of Q fever from (a) unsterilized laboratory clothing, in 6 employees in a commercial laundry (Oliphant, 1949); (b) in two persons in a rooming house involved in laundry, cleaning, and contact with a technician employed where there were seven Q fever infections within 43 days (Beeman, 1950); and in the roommate of a technician during 20 laboratory cases in 90 days (Robbins, 1946). Direct infection of a family member seems to be limited to a very few instances in which the wife has been in contact with the husband during illness or convalescence from a recognized laboratory-acquired infection.

Brucellosis had long been known as a dangerous laboratory agent. But if there was any doubt, it was removed by a report of 94 laboratory-acquired cases during the winter of 1938-39, mostly in students, and probably as a result of aerosols created during centrifugation (Huddleson, 1940). This was followed by a survey by Meyer and Eddie in 1941 (Meyer, 1941). They reported on 76 European brucella infections beginning in 1897, and on 74 lab infections in the U.S. between 1922 and 1939. Again there were no cases in persons who did not work in or visit the laboratory building. My major point from all this, for this audience, is that if no non-laboratory infection occurred with such highly infectious microorganisms as those of Q fever and brucellosis, it certainly will not occur with oncogenic viruses.

In the late 1940s, the USPHS sponsored the first national survey of laboratory infections in the United States. This was published in 1949 by Sulkin and Pike, on 222 viral infections, and was followed in 1951 by an analyses of 1,342 cases collected by a questionnaire sent to 5,000 laboratories (Sulkin, 1951). Only half of the labs replied to the questionnaire. It is more interesting that only 35% of the 1,342 cases had previously been acknowledged by inclusion in a publication (Phillips, 1961). In this regard, what success do you think the National Cancer Institute is going to have, in getting reports of possible laboratory-acquired cancer?

I believe these reports by Sulkin and Pike contributed to decisions in the 1950s, in the U.S. and in several European countries, to modernize labs, or build new laboratories, which could more safely handle infectious agents. The publicity on Biological Warfare also had something to do with these decisions. However, a definite impetus for safer equipment and safer techniques resulted from several surveys on the number of cases of tuberculosis acquired in hospital laboratories and public health diagnostic labs. These surveys during 1940-1957, especially in Sweden, the U.S., Canada, and England, showed that technicians, who were in contact with tuberculous laboratory diagnostic materials or methods, had two to 28 times as much tuberculosis as socially comparable groups (Phillips, 1961). The awareness of the risk of laboratory-acquired tuberculosis was evident in several countries during world-wide personal visits made by Dr. Briggs Phillips.

During the period February 1959 through June 1960, he visited 111 labs in 60 cities in 16 countries. His account has been published (Phillips, 1961). For someone interested in comparing national and institutional policies, attitudes, and approaches to lab safety and occupational health, it is a very interesting document.

II. CAUSE OF LABORATORY INFECTIONS

To summarize data on the cause of laboratory infections in Table 2, I have reworked the data presented by Dr. Sulkin (Sulkin, 1972) in his Tables 2 and 3 so as to show the present comparative importance of the pipette and the syringe. For those of you who are reluctant to stop mouth pipetting, I can point out a unique situation in West Germany. There, a government regulation published in 1956, entitled "Accident Prevention Regulations for Medical Laboratories," which is applicable to all medical, dental, and veterinary laboratories even if infectious agents are not used, (1) prohibits mouth pipetting, and (2) forbids food, drinks, tobacco, and chewing gum in the laboratory. However, personal visits in some of these laboratories in 1960 showed that these regulations were largely unknown or ignored (Phillips, 1961).

The fact that only 30%, of the 3,497 infections reviewed in 1972, could be attributed to a definite cause is no improvement over the 28% attributed to aerosols and accidents in the 1,342 infections reported by Sulkin in 1951. In relation to the cancer program, this can be interpreted to mean that if there are any laboratory-acquired cancers, there is a 70% chance that the actual mechanical or procedural cause will not be known. It is clear that a good accident reporting program is needed.

To get reporting of accidents/exposures, and investigation of unusual illnesses in lab personnel working with oncogenic viruses will not be easy. However, the attitudes of the responsible supervisory personnel among contractors in the virus cancer program is certainly much better than what was sometimes found in European laboratories in 1961. In one instance the interview proceeded as follows (Phillips, 1961).

TABLE 2
Cause of 3,497 Laboratory Infections (mostly acquired after 1930)

	No.	%
Aerosol	466	13.3
Accident	566	16.2
Cut, bite, scratch	192	5.5
Syringe and needle	168	4.8
Spill, spatter	122	3.5
Pipetting	84	2.4
Essentially unknown	2465	70.5
Worked with*	1151	32.9
Completely unknown	782	22.4
Animal/egg/arthropod	532	15.2

* Agent 732, clinical specimen 227, dishwashing 75, human autopsy 69, other 48.

“Case 18—Early on the day of my visit I asked the laboratory director if there had been any laboratory illnesses among workers at the institute. He replied that as long as he had been there he recalled only two laboratory infections. These occurred between 1920 and 1930. One was a syphilitic infection of the finger resulting from a self-inoculation. The other was a case of diphtheria following aspiration of a culture through a pipette.

“We discussed these cases for several minutes. Then the assistant director spoke up and said, ‘Oh yes, we have had two cases of brucellosis in the last two years.’ The causes were not determined.

“Then the director said that he had forgotten about the laboratory epidemic in 1947 in which there were 15 cases of Q fever among workers throughout the building. Recovery was satisfactory in all cases except for the director himself who, following the infection, suffered from pulmonary impairment for three years. No investigation of the Q fever infections was conducted. The worker who everyone thought was responsible left a short time later. The director and his assistant stated that the laboratory man was a ‘sloppy worker’ and that they assumed that he had been centrifuging or grinding tissue.

“I next asked the director (this was still in the morning) if there had been any tuberculosis infections. He replied that there had been no infections and that most operations with tubercle bacilli were relatively safe. At that point the conversation turned to technical aspects of the research with tubercle bacilli.

“In the afternoon, after my lecture, the conversation turned to safe means of challenging animals with infectious aerosols. This conversation prompted the director to remember that there had been some tuberculosis infections. In fact there had been five infections resulting in two

fatalities. One of the cases was the director's wife who had an eye infection and today, as a result, has impaired vision in that eye. Three of the five cases brought suit and were awarded compensation payments (it wasn't clear if the institute or the government paid the compensation). Apparently the infections resulted from experiments in which guinea pigs were being exposed in a crude device to aerosols of tubercle bacilli. No specific investigation was conducted.

"To sum up, at first I was told that there had been only two laboratory infections, but before the day was over I had noted 24 infections in my notebook.

- 1 — Syphilis
- 1 — Diphtheria
- 2 — Brucellosis
- 15 — Q fever
- 5 — Tuberculosis

"Many laboratory directors do not enjoy thinking or talking about their occupational illnesses. I was fortunate enough to win the confidence of some directors and have been told of their past experiences. Even then, however, I have the feeling that directors seldom, if ever, discuss laboratory infections with their staff or with others. Laboratory infections are sometimes skeletons in the closet which are not to be taken out. Few laboratory directors keep written records of laboratory infections."

Pipetting Hazards

A review of five different accident summaries (Table 3) shows that among those laboratory infections associated with reported accidents, about 14% are due to oral pipetting.

TABLE 3
Laboratory Infections Due to Oral Pipetting

Years	Cases with Known Accident	% Due to Pipetting	References
1893-1950	921	17	Reitman, 1955
1930-1950	215	15	Sulkin, 1951; Pike, 1965
1950-1963	156	6	Pike, 1965
1930-1967	165*	13	Sulkin, 1969
1930-1968	460	18	Sulkin, 1969

* Viral and rickettsial

If one reads the accounts of accidents reported in 1915 and recalls recent experience, it is apparent that there has been little change in oral pipetting accidents: the cotton plug is loose and therefore does not stop an onrush of fluid, or a can of unplugged pipettes is absentmindedly selected, or the wrong size pipette is picked up and excessive suction used, or clogged material

in or at the tip of the pipette suddenly is loosed, or the technician has a nose cold that encourages mouth breathing and loss of the usual degree of control of suction, or the pipette inadvertently emerges too soon from the liquid, etc. Such accidents probably are reported infrequently, but from such data as is available, one infection has resulted from each three, or five, reported accidental aspirations (Phillips, 1966). Accidents in Germany (Kisskalt, 1915) with intestinal pathogens showed that infection often could not be prevented by rinsing the mouth with mercuric bichloride, 70% alcohol, or hydrogen peroxide solutions.

In addition to oral aspiration, pipetting can cause human infection by inhalation of aerosols. These are created when drops fall to a hard surface, during forceful mixing by alternate suction and expulsion, by blowing out the last drop, by forceful ejection of a one or 10 ml inoculum into a culture fluid, or by inhalation through an unplugged pipette of aerosol created in the pipette during mixing (Phillips, 1966). Analysis of the particle size of aerosols produced by the first two of these procedures showed the particles to be in the respirable range of 1.0 to 7.5 microns diameter (Kenny, 1968).

A third category of oral contamination arises from placing a contaminated finger on the proximal end of the pipette. Although this is mentioned by several authors (Sulkin, 1963; Reitman, 1955; Phillips, 1966; Darlow, 1969), there seems to be no experimental microbiological data or reported infections from this source. However, it is probable that oral contamination through pipetting was demonstrated long ago by chemists.

Centrifuging Hazards

The centrifuge and its hazards are of special interest in the Virus Cancer Program because the zonal centrifuge can produce a four to five log concentration of the original moderate risk virus material, to get a titer of 10^{11} viral particles or more per ml (Toplin, 1972). No infections of any kind have been attributed to the use of the zonal centrifuge. Nevertheless, the Biohazard Office, through its contractors, is making studies to insure safe operation. From recent progress reports it appears that, when the recommended precautionary measures are taken, the zonal centrifuge will be biologically safer than the more usual laboratory centrifuges. In my opinion, the major danger in the cancer virus program will be not from inhalation of accidental aerosols, but from accidental injection of the concentrate or cut/laceration contaminated by the concentrate.

Accidents with the usual laboratory centrifuge that cause recognized infection seldom occur, in comparison with the syringe and needle, spilling and spattering, pipetting, and bite of animal or ectoparasite (Pike, 1965; Phillips, 1965).

However, a single centrifuging accident with known infectious microorganisms has a much greater potential for causing multiple infections through creation of an infectious aerosol. Four major instances of multiple infection are referenced in Table 4. All these were during 1939-47. Brucella and Q are very durable organisms. The human infectious dose obviously is much lower than that for any cancer virus.

TABLE 4
Infection or Hypersensitivity From Centrifuging Microbial Material

Disease	Comment	Persons Affected	Reference
Allergic attacks	Preparing antigens in a Sharples centrifuge	7	Sulkin, 1951
Allergic attacks	Killed M. tuberculosis	1	Phillips, 1965 (p.144)
Brucellosis	Aerosol spread from basement to 3rd floor	94	Huddleson, 1940
Glanders	Tube broke	3 (2 fatal)	Von Brunn, 1919
Plague	Fluid spun off lip of intact centrifuge tube	1	Burmeister, 1962
Q fever	"use of a centrifuge"	60	Phillips, 1961 (p.45)
Q fever	Spread from 1st to 3rd floor	47	Huebner, 1947
Q fever	Throughout the building "centrifuging or grinding tissue"	15	Phillips, 1965 (p.144)
Tuberculosis	Broken tube and a hole in trunnion cup	2	Phillips, 1965 (p. 144)
Tularemia	"principally the pipetting and centrifugation"	1	Ellingson, 1946
Tularemia	Centrifuging	1	Van Metre, 1959
Western equine encephalitis	"virus was thrown out"	1 (fatal)	Helwig, 1940

Studies with *Serratia indica*, in a standard floor model centrifuge with a slotted swing type head for the trunnion cup, show that a shattered 50 ml centrifuge tube will release about 118 viable microbial-bearing particles per ft³ of room air sampled for 10 minutes at a rate of 1 ft³/min (Reitman, 1966). Other studies have shown that culture spilled on the rotor of a small clinical centrifuge is thrown off in microbial bearing particles that are primarily in the respirable range of 4:0 ± 1.8µ median diameter (Kenny, 1968).

A microbial aerosol also can be spun off from:

1. infectious fluid remaining on the lip of the tube after decantation preceding recentrifugation, as in the case of plague (Burmeister, 1962).
2. leakage of a tube in an angle-head centrifuge caused by the tube being so full that when it attains an angle of less than 45° the fluid reaches the cap, or by distortion of a non-rigid tube as a result of centrifugal force (Darlow, 1969).
3. fluid entrapped in the thread of screw-caps.

In the virus cancer program these aerosols are a potential source for contamination of tissue cultures or other biological materials being used on a nearby unprotected laboratory bench.

The 47 Q fever cases were at NIH in 1945-46, reported by Dr. Huebner in 1947. Actually, in this and other Q fever laboratory epidemics, aerosolization of rickettsia excreted by inoculated animals must have caused some of the infections as well as inapparent infection of some normal animals. This possibility was discarded because attempts to transmit Q fever from infected guinea pigs to normal cagemates had been unsuccessful. There were some serological conversions in guinea pigs but these were attributed to aerosolized yolk sac material, which also was responsible for most of the human infections. It was not until two years or so later that Dr. Huebner's persistent doubt about the exclusion of any cagemate transmission resulted in the discovery that when lethal dosages were used, Q fever was produced almost invariably in control guinea pigs kept in the same room. In 1953 at a Symposium on Psittacosis the significance of the inter-cage transmission and of aerosolized infected yolk sac was stated as follows:

"I should like to see more evidence, based on virus isolation attempts, of the possibility of naturally susceptible hosts developing spontaneous infections in laboratories. Certainly in the psittacosis field this would be indicated. Definitive studies to determine whether spontaneous infections occur in the laboratory seem almost never to be done. This is unfortunate when so much depends on the validity and significance of virus isolation performed in contaminated laboratories" (Huebner, 1955).

These comments also are applicable to the virus cancer program. Fortunately, in this program, there is an active awareness of the need for quality control of animals and biological materials.

III. OCCUPATIONAL DISTRIBUTION OF HUMAN LABORATORY INFECTIONS

For analysis of laboratory infections, by etiologic agent and the laboratory procedure probably responsible for the infection, a good review is available through examination of the 10 tables provided by the late Dr. Sulkin and included in the Manual for this short-course.

Table 5 shows two studies on distribution of cases by occupation: (1) Primary Risk: scientific personnel and assistants; (2) Secondary Risk: animal caretakers, dishwashers, etc.

After review of a large number of case reports on laboratory infections, my estimate is that a comparative attack rate of 0.5 per 1,000 man-years, for the laboratory animal caretaker, and a lesser rate for glassware washers would be appropriate. The infectious risk due to animal handling is difficult to isolate because it is common for animal caretakers to assist in inoculation and autopsy or in other procedures that might cause infection in the absence of a definite accident. In addition to infection from cuts, bites, and scratches there are gastrointestinal infections from manual contamination, and infections from inhalation of aerosolized contaminated animal bedding and excretions. Cases of hepatitis, salmonellosis, brucellosis, and lymphocytic choriomeningitis are prominent. Reported infections of trash handlers and

incinerator operators are very rare, and confined to cases of Q fever: one in a trash collector (Detrick); one incinerator operator at NIH (Hornibrook, 1940); 35 employees in a rendering plant in Syracuse, New York, who processed infected guinea pig carcasses from a laboratory (Feldman, 1950).

TABLE 5
Percentage Distribution of Infection According to Occupation

	Fort Detrick N=369	P& S Survey N=1,286	Attack Rate per Year per 1,000 Persons
Trained scientific personnel	58.5	78.1	1.0
Laboratory technical assistants	21.7		
Animal caretakers	2.1	10.3	0.4
Dishwashers	3.8		
Janitors	0		
Administrative and clerical	3.7		
Maintenance employees	7.8	6.7	1.0
Visitors, friends, etc.	2.4		
Students, not in research	0	4.9	0.1
TOTAL	100.0	100.0	0.5

The occupational epidemiology of laboratory-acquired disease has changed a great deal during the past 20 years because of the increasing number of effective vaccines and antibiotics, improved hygiene, improved laboratory safeguards, and changes in research priorities. However, the microbial world has issued a comparatively new challenge to the research laboratory in the form of viral hepatitis. This virus has until recently confined its laboratory attacks mostly to serum hepatitis (B) in hospital laboratories, diagnostic laboratories, and commercial processors of human blood, and to infectious hepatitis (A) in handlers of subhuman primates. There were 160 cases of the latter reported during 1953-1971 (CDC, 1971). In March 1972 the number of reported overt laboratory-acquired hepatitis infections was given as 84 serum hepatitis and 88 infectious hepatitis (Sulkin, 1972). The successful transmission of human infectious hepatitis from marmoset to marmoset (Deinhardt, 1967), coupled with the recently announced success of research teams at NIH (Feinstone, 1973), Stanford, and AEC in identifying the virus of both infectious hepatitis and serum hepatitis, will result in accelerated research and probably also in some laboratory-acquired infections. From the biohazard viewpoint, there will need to be more emphasis than usual on avoiding hand to mouth contamination, because all experience so far indicates that aerosol transmission of hepatitis has not been important. The glassware preparation area will need special attention. At the NIH the Employee Health Service is aware of the hepatitis problem. Among patient-care personnel of the Clinical Center there were 35 cases of hepatitis from 1 January 1970 to about July 1973. There were four cases elsewhere, two of them associated with handling subhuman primates. It would be interesting to have an epidemiological study of laboratory personnel, particularly those handling blood specimens,

blood transfusions, kidney dialysis machines, and those in laboratories doing basic research on the hepatitis virus.

Further consideration of occupational predisposition to laboratory infection has caused me to wonder what occupation among cancer research personnel might be most likely to produce a laboratory-associated case of cancer. Aside from those who must use a needle and syringe, a group that interests me very much is the pathologists who handle fresh human oncogenic tissue and laboratory personnel who grind and concentrate human autopsy material. The potential hazard for the pathologist is evident from studies on the comparative incidence of tuberculosis. Table 6 shows the results of a careful statistical study of 96 cases of tuberculosis in British medical laboratories during 1949-1953 (Reid, 1957).

TABLE 6
Comparative Incidence of TB in Pathologists

Occupation	Ratio of Observed to Expected Incidence of TB
Male Pathologists	3.2
Post Office professionals	0.7
Male Laboratory Technicians	3.1
Male Post Office Clerks	0.9
Female Laboratory Technicians	1.7
Female Post Office Clerks	0.9

The possibility that a similar occupational group might exist in cancer has led the Biohazard Office of NCI to establish a contract for a feasibility study. This will explore whether meaningful data on the incidence of cancer could be obtained by study of a laboratory population exposed to oncogenic viruses and tissues from cancer patients.

SUMMARY

In concluding this presentation on history and epidemiology of laboratory infections there are a few major points that are worth emphasizing:

1. When a living agent that may cause human disease is studied in the laboratory, it is only logical to expect that sooner or later some laboratory worker will become infected with that agent. Whether or not he has overt illness, or none, and the nature of the signs, symptoms, and clinical course depends upon many unpredictable factors involving the interaction of the host and the agent.
2. It is quite possible that the first proof of a human oncogenic virus will be in the form of disease in a temporarily immunosuppressed laboratory worker accidentally inoculated by the needle of a hypodermic syringe.
3. Analysis of laboratory outbreaks, of multiple infections that have occurred within a few weeks or months in buildings that have had no terminal filtration

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TABLE 10 (Prepared by Dr. Sulkin)

Some Laboratory-Acquired Infections Providing the First Evidence of Infectivity for Man

Agent (Disease)	Year	Comment	Reference ¹
Viruses			
Louping ill	1932	Influenza-like disease followed by encephalitis. Serological confirmation.	Rivers and Schwentker, 1934.
B virus	1932	Bitten by apparently normal <i>Macacus rhesus</i> monkey. Ascending myelitis; fatal.	Sabin and Wright, 1934.
Pseudorabies (Aujeszky's disease)	1938		Tunzman, 1938.
Virus D (Durand's disease)	1939	Febrile illness with viremia.	Findlay, 1942.
Newcastle disease	1943	Acute conjunctivitis and adenitis following accident while working with infected chick embryos.	Burnet, 1943.
Adenovirus, type 3	1953	3 cases with catarrhal and follicular conjunctivitis following accidental infection.	Huebner and Rowe, 1957.
Vesicular stomatitis virus (New Jersey strain)	1954	Viremia associated with respiratory symptoms.	Fellowes et al., 1955.
Rio Bravo	1955	Aseptic meningitis with complicating orchitis. Serological confirmation.	Sulkin et al., 1962.
EAE virus (enzootic abortion of ewes)	1955	Virus isolated from sputum.	Barwell, 1955.
Fowl plague virus	1959	Viremia demonstrated by inoculation of chickens. Only human case recorded in literature.	Steele, J.H., Personal communication.
Zika	1962	Viremia; febrile illness with diffuse maculopapular rash.	Simpson, 1964.
Yaba virus (Simian tumor virus)	1962 (?)	Nodule at site of accidental needle puncture. Virus isolated from tumor.	Grace and Mirand, 1963.
Herpes T (tamarinus) virus	1965	Encephalitis following contact with squirrel monkeys. serological confirmation.	Hull, 1969.
Marburg virus	1967	Several fatal cases from contact with infected blood and tissues of apparently healthy <i>Cercopithecus aethiops</i> monkeys. Agent isolated.	Smith et al., 1967.
EB virus	1967	Viremia; first isolation of agent from clinical case of infectious mononucleosis.	Henle et al., 1968.
Australia antigen	1967	Hepatitis while working with Au suggesting infectious nature of antigen.	Blumberg et al., 1968.
Adenovirus, SV 23	1967	Conjunctivitis following accident with needle and syringe. Only report of human infection with simian adenovirus.	Hull, 1969.
Other Agents			
<i>Coxiella Burnetii</i> (Q fever)	1938	First indication that agent isolated from ticks in Montana was infectious for man. Natural human infection previously recognized in Australia.	Dyer, 1938.
<i>Leptospira ballum</i>	1949	Scratched on finger by infected laboratory mouse. Serological confirmation.	Ruys, C. A., personal communication.
<i>Brucella canis</i>	1968	Pipetting accident; agent isolated from blood.	Carmichael et al., 1968.

¹References listed as presented in original Table; complete citations are not included with this paper.

of air and no primary barriers, shows that no infections outside the building have occurred in persons not associated with the laboratory. In other words, the general public has nothing to fear from diagnostic and research laboratories studying infectious or oncogenic viruses.

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