Epidemiology and Control of Virus Infections in the Laboratory

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Viruses cause some of the most dangerous infections. Laboratory work with viruses entails hazards which should be faced rationally. Data are scarce but studies, particularly of hepatitis, are in progress and are extended to cover other infections also. Surveillance can provide facts with which to correct theories and guide control measures. A simple and informal surveillance scheme operated through membership of a professional association has proved useful and is commended as a model.

The U.S.A. and Britain are among world leaders in concern and arrangements for safety. Safety is an ideal concept, desirable but not attainable in absolute terms. Practical planning for safety is hampered by the fact that safety is not measurable directly but only as the converse of its opposite—in this case, danger. “Safety first” is a useful slogan for propaganda but it is hard to imagine circumstances in life or work where safety has first, as distinct from possibly second, priority. In the real world all options, inaction as well as action, entail some risk and the best we can do is choose wisely to minimize risks. Pursuit of absolute safety as an end in itself is beset with pitfalls and impossibilities. It can be misrepresented by the media, politicians, trade unions, and other interest groups. It creates its own vested interests and industry, organizations, language, and literature to a degree that, by diverting effort and resources, can threaten to obstruct work to conquer real dangers because of purely theoretical hazards of such work. This does not mean that unreasonable risks should be taken, that rational concern and planning for safety are wrong, or that thoughtless and careless working are proper. What is necessary, though often difficult, is to keep in touch with reality and to base policies and procedures on logical consideration of available relevant facts.

One area of concern in recent years has been laboratory work, in particular the hazards of infection to workers and the general public. Traditionally these hazards have been minimized by good technique in the broadest sense—good technique which is necessary for the reliability of the laboratory work itself by avoiding contamination and cross-infection. Some fears are irrational, grounded in superstitious fears and alarmist exaggerations. In the past, a reasonable sense of proportion held among most laboratory scientists in the microbiological field. The majority had ini-
tial training in medicine or veterinary medicine and were familiar with the concepts of asepsis, virulence and pathogenicity, routes of infection, and epidemiology. With this insight and using careful techniques, they experienced fewer accidental infections which resulted in clinical disease than their primitive equipment and facilities might lead today's observers to expect. Despite modern advances, a new danger threatens today since the explosion of methodology in recent years has brought in numerous recruits primarily trained in biochemical and physical sciences, often working with high concentrations of infectious agents but without the basic understanding of infectious processes possessed by their predecessors. This justifies a careful scrutiny and review of "laboratory infections" in the hope of increasing understanding and awareness of infectious hazards and thus improving safety without exaggerated fears or excessive restrictions.

ROUTES OF INFECTION

In the laboratory, as elsewhere, the main routes of infection are (a) percutaneous—overt or inapparent; (b) via mucous membranes contaminated by inhalation, ingestion, or contagion, e.g., by rubbing or splashing the eye.

Airborne Infection

There are numerous sources of aerosols in laboratory work. Some are obvious, e.g., homogenization. Others are less obvious: every make or break of fluid surfaces liberates some droplets. Large particles tend to fall, contaminating surfaces from which they may infect by contact or by resuspension as secondary aerosols. Coarse splashes can obviously contaminate grossly, impinging on surfaces and on the workers whose eyes provide a receptive target draining into the respiratory and alimentary tracts. The smallest particles can remain airborne for long periods, invisible and capable of penetrating deeply into the respiratory tract. If given the opportunity, many pathogens which do not normally spread by respiratory routes can infect in this way. Rational precautions include good, basic technique to minimize the production of aerosols, and sometimes the use of protective devices such as biological safety cabinets and plastic isolators. Unless properly designed, installed, and operated these may give a false sense of security and even increase the hazard. Careful manipulations to avoid generating aerosols in the first place remain essential even when a "safety cabinet" is in use.

Ingestion

Various agents other than those which naturally spread by the fecal-oral route may infect if swallowed, provided they are resistant to the pH, temperature, and enzymes of the upper alimentary tract. Others are too labile, but may yet infect the lips or oropharynx. Given good, basic technique, this route should not provide a hazard—biological materials should never be mouth-pipetted, and obviously one should not smoke, eat, drink, lick the fingers, or put laboratory items in the mouth. Hands should be washed at the end of each laboratory procedure involving infectious agents and protective clothing removed before leaving the laboratory.

Percutaneous Infection

Apparent percutaneous infection resulting from tissue penetration from accidents, particularly those involving sharp instruments or objects, or by gross contamination of an unprotected injury, is an obvious and dangerous hazard. Inap-
parent percutaneous infection constitutes a danger to which attention has only recently become directed by considering the problems of hepatitis B. Whereas in the past infections not obviously due to ingestion or injury tended to be regarded as airborne, the role of inapparent percutaneous infection deserves wider consideration. The practical implications are clear: avoid contaminating the working environment, minimize the use of sharp instruments, and protect the hands by suitable gloves.

Other Routes of Infection

Particular hazards arise in the animal house from pre-established or experimentally induced infections of the animals or their parasites, from scratches, bites, or other injuries, or from contamination by contact, ingestion, or inhalation of infected materials during work with or disposal of the animals. The same routes considered above are involved.

Additional routes not normally relevant in the laboratory include transmission by transfusion and intravenous injection, by transplantation of tissues or organs, and by intimate personal contact particularly involving mucosal surfaces. Laboratory workers are exposed to these other mechanisms of infection during their normal life in the community, and the probable importance of non-occupational factors emerged during studies of hepatitis B in clinical laboratory staff [1,2].

RECENT OBSERVATIONS

A large body of evidence about laboratory infections was amassed by Pike, who analyzed world experience since the beginning of this century [3]. The data were heavily weighted by events before the era of chemotherapy and by the changing pattern of research on different groups of infectious agents over the period. The populations at risk were unknown and attack rates could not be calculated. Despite these limitations, the importance of certain factors emerged clearly. For instance, accidents, particularly those involving skin penetration or exposure to aerosols, were important. The most hazardous class of activity was “research” which accounted for more than half of the infections. It is interesting that whereas rabies and smallpox have both caused accidental infections during research [4–6] or vaccine production [7] neither, to my knowledge, has done so as a result of the numerous diagnostic tests for these viruses carried out for many years on a large scale in laboratories all over the world, often with only simple facilities. No doubt immunization often reduced the risks, but not completely in these four incidents.

Several surveys in Britain concentrated essentially on clinical laboratories. Surveys by Harrington and Shannon between 1971 and 1974 revealed a pattern of sickness absence and accidents similar to other working populations but with less sickness absence than other comparable occupational groups [8–10]. Excess tuberculosis, diarrhea, dermatitis, hepatitis, and shigellosis were found in the laboratory group.

Hepatitis

A series of surveys by questionnaire to members of the Association of Clinical Pathologists concentrated on hepatitis. Since both numerators (cases of hepatitis) and denominators (staff numbers in employment categories and laboratory disciplines) were obtained, valid attack rates could be calculated to allow comparisons of incidence in various groups and trends over the years. Crude attack rates showed a marked fall from 123 per 100,000 person years in 1970–1974 to 27 in
1975-1979 [2,11]. The highest sustained rates involved biochemistry and hematology workers, and only in these groups of bench workers were cases reported after 1974. Follow-up of the 18 cases reported in 1975-1979 showed two altered diagnoses. Of the remaining 16, six were confirmed acute hepatitis B infections by all laboratory criteria, five with histories suggesting non-occupational sources of infection. Three other presumed acute hepatitis B infections were not followed through to the disappearance of HBsAg or acquisition of antibody. The remaining seven gave negative tests for hepatitis B and comprised presumed hepatitis A and “Non-A Non-B” infections. Details were given in the ten-year summary [2].

Laboratory staff accounted for only 0.5 percent of hepatitis B infections reported to the Communicable Diseases (Scotland) Unit in 1976-1979 and recorded for the rest of Britain during 1972-1979 in Communicable Disease Reports [12,13] and the marked decline after 1974 is reflected in these independent data. Since there had been neither time nor resources to introduce by 1975 the strict control measures recommended by the “Howie Report” [14] which was not published until 1978, the improvement must surely have been due to increased awareness of risk and improvements in operating procedures following other reports [15,16]. Since hepatitis B spreads within laboratories by the parenteral route and yet few of the cases reported overt injury or accident, it seems likely that inapparent routes of parenteral infection were important. Confirmation of widespread contamination within laboratories testing infected specimens and using automated apparatus was published by Lauer et al. in the U.S.A. [17] and in Britain by Newsom and Matthews [18]. It is hardly surprising, therefore, if careful working to minimize contamination together with minimal use of sharp instruments and protection of skin by disposable gloves suffice to control the hepatitis B risk almost completely. The value of distinguishing “high-risk” specimens by special labeling is doubtful if it gives a false impression that unlabeled specimens can safely be handled casually! Dangerous assumptions that materials not categorized as dangerous were therefore “safe” led to the Marburg incident [19] and to an instructive accidental infection with trypanosomes in Glasgow [20,21] which was critically discussed in an accompanying editorial [22]. In this latter case although the agent was thought to be non-infective to man, the worker was a student (albeit medical), the work was a research procedure using high concentrations of the organism, and ungloved hands and fingers scratched by restraining the animals were exposed to contamination—a dangerous combination of risk factors!

Other Infections

Pike reported a downward trend of laboratory-associated infections other than hepatitis in recent years [23]. Extension of the British survey in 1979 to include other infections as well as hepatitis revealed nine airborne infections (five tuberculosis, four varicella), five enteral infections (four salmonella or shigella infections and one case of hepatitis, not B, acquired on holiday), and one parenteral infection with malaria [24,25]. This survey is being continued to collect sufficient data to allow valid attack rates to be calculated and reveal trends and differences as was done for hepatitis. A striking feature in 1979 was that, unlike hepatitis, these other infections mainly involved microbiology workers, suggesting scope for improvement in technique and perhaps facilities. Recent experience in the U.S.A highlighted the infectiousness of S. typhi, most infections with which now result from work with known cultures for instructional or quality-control purposes [26]. Tuberculosis is a well
recognized hazard from sputum but a recent study in London [27] revealed the increasing importance of extra-pulmonary tuberculosis and of other types of specimen such as pus and urine. The postmortem room and animal house also remain areas of risk from tuberculosis [24] as well as many other infections including viral zoonoses.

Virus infections have not been prominent in recent British experience of laboratory infections, though they include those pathogens classified as the most dangerous. Work on highly dangerous pathogens is now strictly regulated in most countries, but rules and regulations can be defeated by human error, gadgetry may break down, and in the last analysis it remains essential that those working with such pathogens remember and maintain good, and therefore safe, technique. Although two incidents of smallpox infection from laboratories in Britain stimulated much of the recent public and professional alarm about the dangers of such work, the main lesson of the 1973 incident is the inadvisability of allowing visits by unvaccinated persons while the work is in progress; despite generally unsatisfactory conditions found by the subsequent enquiry [4] smallpox had not in fact “escaped” until then. In spite of delay in clinical recognition of the case, the efficiency of control measures was highlighted since no further spread occurred after the secondary cases were diagnosed. Likewise no secondary cases arose from the episode in Birmingham in 1978 where again large amounts of infective virus were being worked with under conditions which had become unsatisfactory long before infection “escaped.” Which if any of the faults then found was responsible for this infection or whether some undetected and possibly human factor was involved remains uncertain. Fortunately not every particle or droplet arising from infectious materials contains viable pathogenic organisms; only a minority of virions are infective and not all of these survive into the final inoculum, not every inoculum reaches receptive tissues, natural defenses remove or destroy much of the challenge inoculum, not all of those viable virions which reach the host’s tissues make contact with the appropriate receptors of a receptive host cell, and probably not every infective process initiated in one cell successfully establishes a spreading infection in the host.

DISCUSSION

“The price of liberty is eternal vigilance,” and this is true of laboratory infections. The relevant vigilance is based on informed awareness of the materials and possible pathogens under study, of the working environment, equipment, and procedures, of possible and expected hazards. It includes proper organization of the work with appropriate “safety measures” including immunization where appropriate, and organized surveillance and vigilance at laboratory and community levels to monitor infections possibly attributable to laboratory work by clinical and even serological observations. Life and work are inevitably dangerous, and this is also true of microbiological work for which professional fitness includes the necessary understanding and training directed to minimize risks and maximize safety. This is particularly important for the rising generation of young researchers who may work with high concentrations of infectious agents by chemical and molecular biological techniques. Unnecessary fears may arise if the realities of epidemiology, transmission routes, and pathogenic mechanisms are unfamiliar. Alternatively there may be dangers from casual and careless working by those who are ignorant of the risks.

Finally, where a problem is so bedevilled with ignorance and misunderstanding based largely on theorizing without data, epidemiologically sound facts are badly required. The ongoing survey, initially of hepatitis, organized through the member-
ship of the Association of Clinical Pathologists and now extended with the help of the Joint Working Party of the Royal College of Pathologists, Institute of Medical Laboratory Scientists, Association of Clinical Biochemists, and Association of Clinical Pathologists to cover other infections is commended as an example of a simple mechanism capable of collecting valid data rapidly and without the distortions which sometimes reduce the significance of more formally collected information.

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