Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™
Morbidity and Mortality Weekly Report (*MMWR*)

Laboratory Contributions to Public Health

Supplements

October 7, 2011 / 60(04);27-34

Walter R. Dowdle, PhD[1]

Leonard W. Mayer, PhD[2]

Karen K. Steinberg, PhD[3]

Neelam D. Ghiya, MPH[4]

Tanja Popovic, MD, PhD[4]

[1]*Global Polio Eradication, Task Force for Global Health, Decatur, Georgia*

[2]*Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, CDC, Atlanta, Georgia*

[3]*Division of Laboratory Sciences, National Center for Environmental Health, CDC, Atlanta, Georgia*

[4]*Office of the Associate Director for Science, Office of the Director, CDC, Atlanta, Georgia*

Corresponding author: Walter R. Dowdle, PhD, Task Force for Global Health, 325 Swanton Way, Decatur, GA 30030; Telephone: 404-687-5608; Fax: 404-371-1087; E-mail: wdowdle@taskforce.org.

Introduction

Alexander Langmuir, founder of the CDC Epidemic Intelligence Service (EIS), was quoted in the early 1960s instructing incoming EIS officers that the only need for the laboratory in an outbreak investigation was to "prove their conclusions were right." Understandably, this was not well received by the CDC Laboratory Branch. However, Langmuir's point was not to denigrate the laboratory but to emphasize the power of an investigation based on a solid clinical case definition and established field epidemiologic principles. In truth, in 1960, when CDC assumed responsibility for publishing *MMWR*, the laboratory provided little added value in many investigations, except to confirm "what the etiologic agent wasn't." Existing diagnostic laboratory procedures for infectious and noninfectious diseases of public health importance were reasonably reliable but basic and laborious. For diagnosis

of many diseases and conditions, no laboratory procedures existed. Since 1961, advances in molecular sciences, analytical chemistry, and technology have revolutionized the public health laboratory investigative capacity, capability, and specificity and have emphasized the importance of more independent laboratory research. The term "molecular epidemiology" is widely applied, and the number of diseases for which laboratory diagnoses are available today is substantially larger. This article describes the principles and practices of the state-of-the-art public health laboratory in 1961 and provides examples of scientific, technologic, and strategic advances since that time that characterize the still evolving public health laboratory of the 21st century.

Browsing through *MMWR*, volume 10, week 1, January 13, 1961, provides insight into the public health laboratory of 1961 and the topics of most interest and visibility at that time. Subsequently, progress and contributions made by the public health laboratories are provided in a more detailed account by using several illnesses and conditions of public health importance as examples. They span both infectious and noninfectious arenas. Some were listed in the first *MMWR* summary, but some were not under consideration in 1961 or were yet to be discovered.

The Public Health Laboratory of 1961

Poliomyelitis (3,190 cases in 1960) was the first disease discussed in the Summary section of the January 13, 1961, *MMWR* (*1*). The basic procedures for isolation and identification of polioviruses in cell cultures were slow but well developed, benefitting from 30 years of concentrated laboratory research to understand the disease and develop a vaccine. Week 33 published the Surgeon General's announcement that a license had been granted to Pfizer Inc. for the manufacture of the Sabin live oral polio vaccine (OPV) type 1. This attenuated strain was developed in the CDC laboratories in Montgomery, Alabama. Although a remarkable humanitarian achievement, the introduction of live vaccine into the environment and the clinical and epidemiologic need to differentiate vaccine strains from wild strains proved a major challenge to the laboratory.

Hepatitis was the second viral disease in the Summary section. The national hepatitis epidemic occurred in 1961. Shellfish were implicated for the first time. The laboratory was of little help because the etiologic agents were unknown. Outbreaks were differentiated into infectious or serum hepatitis on the basis of clinical and epidemiologic grounds, and the totals (72,651 cases in 1961) were combined.

Influenza A2 was the third disease noted in the Summary section. Because development of an influenza virus vaccine had been a high priority of the U.S. military during World War II to avert another 1918 disaster, basic procedures for virus isolation and serologic diagnoses were well established. Classification according to H (hemagglutinin) and N (neuraminidase) antigens was yet to come.

Rabies was a notifiable disease in humans and animals, with three and 3,599 cases reported, respectively, in 1961 (*2*). Diagnostic procedures were evolving from the traditional histologic staining for Negri bodies to specific fluorescent antibody staining, greatly increasing confidence in laboratory diagnosis.

Anthrax, commonly known as "wool-sorters disease," totaled 14 cases in 1961 (*2*). The laboratory diagnosis of *Bacillus anthracis* was based on traditional microbiologic methods, some of which are

still the cornerstone of laboratory diagnostics today: staining with the M'Fadyean polychrome methylene blue stain (developed in 1903) and susceptibility to lysis by the gamma phage (since 1951). Human vaccines for anthrax had already been developed in the United Kingdom and the United States. There were no prescribed special biosafety laboratory facilities.

Outbreaks of salmonellosis, shigellosis, staphylococcal food poisoning, pathogenic *Escherichia coli*, typhoid fever, and botulism were commonly reported in volume 10, week 1. Mingled among these reports were 25 apparent foodborne disease outbreaks of unknown etiology by mid-year. The need for discovery of new and more precise characterization of already recognized etiologic agents of diarrhea was evident.

Listed clinical conditions of unproven etiology included rubella, erythema infectiosum, and cat-scratch fever. Yet to come were rotavirus, *E. coli* O157, and HIV infections; Legionnaires disease; hemorrhagic fevers; and severe acute respiratory syndrome, to name a few. Roseola infantum, now known to be caused by one of eight human herpesviruses (type 6), exemplifies the progress made during the past 50 years. Only one (herpes simplex virus) was recognized in 1961.

Except for one naturally occurring nicotinic acid (niacin) toxin, *MMWR* contained no reports on noninfectious diseases. However, in 1961, CDC began a collaboration with the National Heart, Lung, and Blood Institute to expand the Cooperative Cholesterol Standardization Program with a goal of standardizing cholesterol measurements and, ultimately, decreasing deaths and disability from heart disease.

The following sections review these and other diseases and provide some insight into the scientific and technical advances that have revolutionized the public health laboratory capabilities during the past 50 years.

Poliomyelitis

The inability in 1961 to distinguish clearly between epidemic wild strains and attenuated OPV strains recovered from fecal samples led to numerous disagreements among advisory bodies on the etiology of potential cases of vaccine-associated poliomyelitis. The biology-based laboratory test then in use also figured prominently in the 1974 landmark legal ruling (*Reyes vs. Wyeth Laboratories*) on the liability of the manufacturer for failure to warn the public of OPV risks (*3*), despite the epidemiologic and biologic laboratory evidence that the causative virus was most likely wild. More reliable nonbiologic laboratory techniques were needed. By 1984, the laborious but definitive newly developed oligonucleotide fingerprinting technique confirmed the Reyes poliovirus isolate as wild (*4*).

The growing capabilities of the poliovirus laboratory coincided with the launch of the global polio eradication initiative in 1988. Continuously evolving molecular techniques and novel technologies eventually made possible the sequencing and comparing of poliovirus genomes in real time. Linking these advances to the newly established poliovirus evolutionary rate provided previously unimagined detailed information about individual poliovirus isolates. In 2000, genome sequencing identified the first outbreak of circulating vaccine-derived polioviruses, which continue to occur in areas with low rates of OPV coverage and document the urgent need to replace live with inactivated (killed) poliovirus vaccine (IPV) (*5*).

The 2010 *MMWR* report on polio eradication progress illustrates current laboratory capabilities (*6*).

The Islamabad, Pakistan, polio laboratory, one of 147 laboratories in the polio network, processed >15,000 fecal and sewage samples and isolated 137 polioviruses in 2009. Genomic sequencing of these 137 isolates from Afghanistan and Pakistan provided data that identified virus origins, transmission zones of circulating wild viruses, and viruses that were not closely related. Information about virus origin and transmission inform the program of inadequately immunized populations. Distantly related viruses provide evidence of evolutionary gaps and inform the program of surveillance weaknesses that must be improved. Molecular epidemiology plays a key role in all aspects of the poliovirus eradication initiative.

Hepatitis

In 1961, a report of an outbreak of infectious hepatitis A among chimpanzee handlers (*7*) generated considerable interest, suggesting nonhuman primates might be possible models for human hepatitis. However, 18 years would pass before the virus would be propagated in cell culture, which would make laboratory diagnosis and a vaccine possible (*8*). In 1963, the serendipitous discovery of an antigen in human blood (*9*) led to the eventual association of this protein with serum hepatitis B and development of a highly effective vaccine in the early 1980s. The development of diagnostic tests for hepatitis A and B viruses led to recognition of three other etiologic agents (types C, D, and E). In few other infectious diseases has progress been as rapid and effects on disease reduction as dramatic.

Influenza

In 1961, lessons learned from the overwhelming laboratory workload during the A2 pandemic of 1957--58 were still being implemented. Expanded serologic diagnostic tests were being introduced for other newly recognized agents of acute respiratory disease (parainfluenza, respiratory syncytial virus, and adenoviruses). The workhorse complement fixation (CF) serologic test deserves special mention to illustrate the labor-intense laboratory practices of the day. The test was performed over a 3-day period in a large room with two big tables specially designed for the purpose in the new (1960) virology laboratory building. The average run of paired serum samples from 50 patients used approximately 4,000 test tubes (all to be washed and reused), 60 wire test tube racks, and nearly 100 pipettes. On day 1, six antigens were prepared, test tubes marked, and serum sequentially diluted (by mouth pipette). On the morning of day 2, the four essential test reagents were prepared and standardized. In the afternoon, 8--10 laboratory personnel were rounded up; given instructions and pipettes; and marched around the table adding one ingredient in precise sequence. The racks were moved to a walk-in refrigerator. On the morning of day 3, the final indicator reagent was added and the results read, tube by tube, against the ceiling lights, trusting no one had added materials to the wrong test tubes or in the wrong sequence. Another 4 years would pass before that resource-intensive CF procedure would be aided by microtechniques and, later, by automatic pipetting machines (Figure 1).

Today, the CF test is rarely employed, but other serologic tests (neutralization and hemagglutination-inhibition), also used in 1961 to detect and quantify antibodies in patient's serum, remain in principle unchanged. The greatest advances in understanding the influenza virus closely parallel the phenomenal advances in molecular technology. Definitive characterization of influenza viruses, as in all other areas of virology, relies heavily on genome sequencing. The pandemic virus of 1918 was reconstructed by reverse genetics and genomic RNA recovered from archived formalin-fixed lung autopsy materials and from an influenza victim buried in the permafrost (*10*). The pandemic

influenza A (H1N1) 2009 virus was demonstrated to be a triple genetic reassortant with an antigenic structure similar to those of the influenza viruses circulating early in the 20th century (*11*). Yet to benefit from these major breakthroughs in science is the killed influenza vaccine, which has seen only incremental improvements since 1961.

Anthrax

Major advances in the laboratory identification of *B. anthracis* were made during the 1980s by sequencing the structural genes located on one of the plasmids, pXO1, and encoding the three anthrax toxins (*12*). However, the real scientific renaissance of *B. anthracis* began in the mid-1990s as inhalation anthrax became the initial focus of the laboratory component of biothreat preparedness in the United States. Development of new diagnostic and molecular subtyping tools with emphasis on standardization and quality control led the path for establishing the Laboratory Response Network that was instrumental in analyzing approximately 200,000 environmental and clinical specimens during the 2001 anthrax attacks (*13*). Polymerase chain reaction (PCR) detecting three *B. anthracis*--specific loci allowed for rapid (a few hours) identification of this organism directly from clinical specimens. Multiple locus variable-number-of-tandem-repeat analysis (MLVA) made differentiating the *B. anthracis* strain and implicating the Ames strain in 2001 possible. Identification of an identical MLVA type in the clinical specimens of the patients and at their respective infection sources (e.g., offices, post offices) provided the laboratory confirmation that the events were intentional and not a result of natural exposure (*14*).

Laboratory research on *B. anthracis* continues post 2001. Although the first report of naturally occurring anthrax toxin genes in a species (*B. cereus*) other than *B. anthracis* adds complexity to the identification process, it also emphasizes the importance of vigilance and close collaboration between those treating the patients, the public health community, and the research community in ensuring that the true causative agents are identified rapidly and reliably (*15*).

Rapid detection in clinical specimens and molecular subtyping of biothreat agents, which were demonstrated to be of critical importance for public health response in 2001, are now the standard in approximately 150 Laboratory Response Network laboratories in the United States and worldwide. This ancient disease is likely to continue to shape research and public health future issues.

Foodborne Diseases (PulseNet)

Methods for characterizing etiologic agents of diarrhea, such as multilocus enzyme electrophoresis and ribotyping, first became available and used during the 1980s. However, no method was broadly accepted and standardized for use on different organisms until after the *E. coli* experience of the early 1990s.

From November 1992 through February 1993, approximately 700 laboratory-confirmed infections with *E. coli* O157:H7 occurred in Washington, Idaho, California, and Nevada associated with ground beef. Distinct clinical presentation associated with this pathogen was first described in 1983 and subsequently recognized as an important cause of bloody diarrhea and the most common cause of renal failure in children (hemolytic uremic syndrome) (*16*). During the 1992--93 outbreak investigations, CDC used pulsed-field gel electrophoresis (PFGE) to characterize clinical and food isolates and distinguish outbreak-related and nonoutbreak strains (*17*). To satisfy the subsequent enormous nationwide demand for PFGE subtyping, standardized methodology was transferred to

four state public health laboratories in 1995. This national molecular subtyping network for foodborne disease surveillance later became known as PulseNet (*18*) and was officially launched in 1998 by the White House.

PFGE continued to be an indispensable tool in a number of *E. coli* O157 outbreaks. Over time, the primary role of PFGE and PulseNet gradually shifted from a tool to investigate and compare outbreaks to a real-time surveillance, cluster-detection, and outbreak investigation system. One such PulseNet-detected outbreak in Colorado in 1997 resulted in the largest meat recall thus far (*19*). PulseNet quickly expanded to include other etiologic agents of foodborne diseases: *Salmonella* and *Shigella* spp, *Listeria monocytogenes*, *Campylobacter jejuni*, *Vibrio cholerae*, and *Yersinia pestis* (www.cdc.gov/pulsenet) and has gone on to receive awards as one of the most innovative government programs.

The impact of PulseNet on the nation's health has been enormous. PulseNet has been instrumental in improving foodborne disease surveillance and outbreak investigations, especially outbreaks in which the cause might be the same but affected persons are geographically far apart. Outbreaks and their causes now can be identified much faster. Critically important is the PulseNet approach to building public health infrastructure in state and local health departments with methods, equipment, and training that can be used broadly. Geographically localized outbreaks are no longer the norm. Foodborne illnesses do not respect borders. Food distribution, preparation, and consumption practices have changed worldwide during the past few decades so that food produced and prepared in one place can be sold and consumed worldwide. Consequently, PulseNet International, a network of national and regional laboratories, was created to track foodborne infections worldwide. Each laboratory uses standardized methods and shares the information within the network in real time. PulseNet is committed to introducing new and improved subtyping methods and strengthening collaboration with the food industry to prevent outbreaks.

At the time of the first *MMWR* publication at CDC in 1961, little was known about viral agents as causes of enteric diseases. Soon thereafter a number of viruses were identified, detected in patients' fecal specimens, and associated with clinical symptoms: during the 1960s, enteric adenoviruses and Norwalk virus (presently defined as noroviruses and belonging, along with the saporovirues, in the *Caliciviridae* family) and in the 1970s rotaviruses, caliciviruses, and astroviruses (*20*). Today, noroviruses are recognized as the most important causes of nonbacterial epidemics of gastroenteritis; rotaviruses account for almost one third of all diarrhea-related deaths in children aged <5 years worldwide; and since 2006, two new safe rotavirus vaccines have been licensed. Feces remains the main clinical sample, and available laboratory diagnostic tests range from isolation of viruses in cell culture to direct visualization of viruses in clinical specimens (e.g., electron microscopy) to detection of viral antigens (e.g., enzyme-linked immunosorbent assay) to detection of viral nucleic acid (e.g., PCR).

Legionnaires Disease

In July 1976, the disease became a household word when approximately 200 American Legion conventioneers in Philadelphia were stricken, resulting in 34 fatalities (*21*). Initial media speculation focused on swine influenza, which had caused an outbreak in Fort Dix, New Jersey, and media excitement earlier in the year. An extensive epidemiologic investigation indicated airborne transmission of an agent in the environment, but the inability of the state and CDC laboratories to

identify quickly an infectious etiologic agent intensified media attention and speculation about other sources, including heavy metals or other poisons such as paraquat and even terrorism. During fall 1976, a team of nationally recognized pathologists visited CDC and reviewed clinical findings, autopsy materials, and tissue sections and concluded the causative agent could be a virus or a toxin but not a bacterium, illustrating the pitfalls of using conventional techniques to identify an unknown, unconventional agent. In December 1976, CDC identified the agent as a bacterium that could not be detected by using ordinary tissue staining (*22*) (Figure 2). Tissues from Guinea pigs inoculated with patient specimens showed small pleomorphic rods by fluorescent antibody staining by using convalescent serum. The bacteria were initially grown in eggs injected with tissue from Guinea pigs and eventually on microbiologic media, allowing production of reasonable amounts of materials for other studies.

The initial reports and presentations by CDC describing the etiologic agent were met with considerable skepticism and disbelief, but the etiology and the name *Legionella pneumophila* became accepted as outbreaks were reported by others. The identification of *L. pneumophila* as a new species of bacteria was determined by using DNA--DNA hybridization (*23*). Today, the genus *Legionella* contains 48 species, 20 of which have been shown to cause human disease.

Outbreaks occurring as early as 1957 were retrospectively associated with serologic evidence of Legionnaires disease (or legionellosis). After *L. pneumophila* was identified and this bacterium was delineated as a common cause of pneumonia, several outbreaks have occured around the world, some as large as 800 cases. Retrospective examples of legionellosis include an outbreak of pneumonia among patients of the St. Elizabeth's Psychiatric Hospital, Washington, D.C., during 1965 with 94 cases and 16 deaths. Another form of this disease was shown in visitors to and employees of the Pontiac, Michigan, health department in 1968 with 144 cases of fever, headache, myalgia, and fatigue without pneumonia, resulting in no fatalities (*24*). In addition to these serologic investigations that used microbiologic analysis of bacteria stored at CDC, an unclassified agent isolated in 1947, was shown to be identical to *L. pneumophila* by serologic, cultural, and DNA relatedness studies. In these situations, the maintaining of large patient specimen collections, serum banks, and culture collections was shown to be of great value.

Although the bacterium is widespread in many freshwater environments, the disease is usually associated with human-made water systems, such as cooling towers, air conditioning, fountains, spa baths, and water supply systems of buildings (including showers). Although culture remains the standard, PCR is increasingly used to detect *Legionella* spp. (*25*). Understanding the modes of transmission and epidemiology of legionellosis has resulted in major changes in construction and maintenance recommendations for municipal, commercial, and residential water systems.

Noninfectious Diseases

The inaugural CDC *MMWR* volume was devoted almost exclusively to infectious diseases. Even at the time, however, CDC and other laboratories were engaged in noninfectious disease research that would make major contributions to the identification and prevention of chronic, newborn, and environmental diseases and conditions. Examples include 1) standardizing cholesterol measurements that enabled longitudinal studies to establish the causal link between cholesterol levels and cardiovascular disease (CVD); 2) identifying lead in gasoline as a major source of lead exposure for children and adults; 3) characterizing exposure to tobacco smoke and its toxic constituents in

smokers and nonsmokers; and 4) developing methods and providing quality assurance for screening for conditions and diseases of newborns.

CVD remains the leading cause of death in the United States, with reduction of low-density lipoprotein ("bad") cholesterol a major public health priority to prevent CVD and death (*26*) (Figure 3). In 1957, CDC began collaboration with the National Heart, Lung and Blood Institute to develop a standardization program for total cholesterol measurements. The initial program, called the Cooperative Cholesterol Standardization Program, was later expanded to include triglycerides and high-density lipoprotein ("good") cholesterol and renamed the Lipid Standardization Program. These programs had a goal of standardizing lipid and lipoprotein measurements and, ultimately, decreasing deaths and disability from heart disease (*27*). CDC's cholesterol reference method has served as the standard for cholesterol testing for approximately 35 years and was essential to provide the accuracy base for cholesterol measurements in the major epidemiologic studies and clinical trials that established the relationship between cholesterol concentrations and risk for CVD (*28*). In addition to the Lipid Standardization Program, CDC continues to standardize a network of five laboratories that use the CDC accuracy base to calibrate measurement of high-density liproprotein cholesterol, low-density liproprotein cholesterol, and total cholesterol by commercial instrumentation in the clinical laboratories that measure the lipid levels of Americans.

Lead exposure is one of the oldest known environmental and occupational hazards, but not until the early 1970s was relatively low-level exposure recognized to cause neurodevelopmental impairment in children (*29*). Using highly precise and accurate atomic absorption methods, CDC measured blood lead levels in the U.S. population as a component of CDC's National Health and Nutrition Examination Surveys during 1976--1980 (*30*) and identified lead in gasoline as a major exposure source for children and adults. This new and unexpected finding was a major factor in the U.S. Environmental Protection Agency's decision to remove lead from gasoline, an effort that has been cited as one of the most important accomplishments of public health (*31*). Accurate blood lead measurements in the National Health and Nutrition Examination Surveys documented that the removal of lead from gasoline resulted in a >90% decrease in the percentage of children with blood lead levels ≥10 μg/dL, the current level of health concern (*32*,*33*). These data supported removal of lead from gasoline in industrialized nations around the world, resulting in similar reductions in lead exposure.

Development of methods to quantify approximately 100 addictive and toxic constituents of tobacco products led to an especially sensitive and accurate measurement for serum cotinine to quantify tobacco smoke exposure in smokers and to nonsmokers exposed to secondhand smoke. Evidence that 88% of nonsmokers were exposed to secondhand smoke was used during the early 1990s to justify restricting smoking in public places and in the workplace (*34*). Follow-up of cotinine measurements documented the reduction in average cotinine levels for nonsmokers by approximately 70% (*34*). CDC measurements of addictive and toxic constituents of tobacco products, including tobacco-specific carcinogens, are the major science underpinnings for regulation of tobacco products.

CDC standardizes diagnostic methods for >50 diseases of newborns, ensuring the quality of measurements performed on heel-stick blood spot specimens from >98% of all babies born each year in the United States. Laboratory measurements for early diagnosis usually lead to effective early treatment of many diseases, including congenital hypothyroidism, congenital toxoplasmosis,

galactosemia, congenital adrenal hyperplasia, sickle cell disease, maternal HIV infection, cystic fibrosis, fatty acid oxidation disorders, and amino acid disorders.

CDC characterizes exposure of the U.S. population and vulnerable population groups to environmental chemicals known or suspected to cause health problems (*35*). CDC can currently measure 396 environmental chemicals in blood or urine---with future plans to expand to more than 500. Studies of human exposure and health effects particularly benefit from CDC blood and urine measurements of these chemicals. In addition, to bolster emergency response for chemical and radiologic terrorism, CDC has developed capability to measure, in blood or urine, 150 chemical agents and nine radionuclides that are priority terrorism agents. Future plans include expansion of these capabilities, with special focus on measuring additional radionuclides.

The Public Health Laboratory of the Future

The disease triangle is the basic tenet for causation of infectious disease representing the interaction between three entities: environment, pathogen, and host. Chronic diseases are generally caused by the interaction of host factors and the environment, including lifestyle factors and diet, with pathogens sometimes playing a causative role---for example, human papillomavirus linked to cervical cancer and *Helicobacter pylori* linked to the development of duodenal and gastric ulcers and stomach cancer. Advances in laboratory sciences, including informatics and bioinformatics, molecular biology and genomics, nanotechnology and technologies yet to come will facilitate understanding of causation and epidemiology of infectious and chronic diseases that threaten the public's health.

Enormous progress has been made since the central dogma of molecular biology (DNA to RNA to protein) was elucidated some 50 years ago, and revised in 1970 with the discovery of reverse transcription (*36*). Many new "-omics have appeared," including genomics, proteomics, glycomics, metabalomics, and, transcriptomics. A Google search yielded about 60 million results for the term genome (*37*) alone. The development of the PCR, for which Kerry Mullis won a Nobel Prize in 1993, made sequencing the human and other genomes feasible (*38*). Soon, single-molecule DNA sequencing will make it possible to envision whole genomes, including the human genome, to be sequenced in 1 day at a cost of <$1,000 (*39*). Bioinformatics has made it possible to exploit these techniques, generate algorithms, and rapidly analyze complex laboratory and epidemiologic databases to identify virulence factors in infectious diseases and detect biomarkers at the earliest stages when diseases can be reliably predicted and prevented.

The laboratory of the future will build on the work being done today in miniaturization and nanotechnology, considered to be the third industrial revolution. Miniaturization of laboratory instruments at the point-of-care will allow public health workers to obtain patient data in remote places. Ultrasensitive immunosensors and arrays based on nanotechnology will have the ability to quantify protein concentrations at the level below micrograms/deciliter (*40*). Urinary tract infections will be identified at the bedside in remote regions with miniaturized electrochemical biosensors (*41*).

Continued advances in laboratory science and informatics are critically important for all aspects of public health, especially for public health surveillance where informatics is essential for defining the baseline information about human health and for evaluating progress. However, care must be taken that the application of newer laboratory techniques and more sophisticated health informatics introduced for the good of public health do not also bring unintended harm. Society must judge the

ethics of implementing the scientifically possible, whether it is the personal risk of the use of nanoparticles or the privacy risk of placing a patient's genome in an electronic record.

Conclusions

Enormous advances have been made in the public health laboratory in the past 50 years, greatly expanding disease knowledge, revolutionizing diagnostic and surveillance relevance and capacity, and facilitating appropriate control strategies. From limited biologic capabilities, today's public health laboratory routinely uses a multitude of molecular technologies and electronic applications. From a small number of laboratories with primarily an infectious disease focus, today's public health laboratory is responsible for emergency preparedness and response, environmental health, food safety, global health, infectious diseases, informatics, laboratory systems and standards, genetics and newborn screening, and research. From a narrow local, state, or national perspective, today's public health laboratories are recognized as essential components of a vital national and global surveillance system. The next 50 years are anticipated to be equally exciting and the young public health practitioners will see and benefit from this progress.

References

1. CDC. Provisional information on selected notifiable diseases in the United States and on deaths in selected cities for week ended January 7, 1961. MMWR 1961;10:2.
2. CDC. Reported incidence of notifiable diseases in the United States, 1961. MMWR 1962;11(Suppl).
3. Mann ME. Mass immunization cases: drug manufacturers' liability for failure to warn. Vanderbilt Law Review 1976;29:235--66.
4. Kew OM, Nottay BK. Molecular epidemiology of polioviruses. Rev Infect Dis 1984;6:499--504.
5. Kew OM, Sutter RW, de Gourville EM, Dowdle WR, Pallansch MA. Vaccine-derived polioviruses and the endgame strategy for global polio eradication. Annu Rev Microbiol 2005;59:587--635.
6. CDC. Progress toward poliomyelitis eradication---Afghanistan and Pakistan, 2009. MMWR 2010;59:268--72.
7. Hillis WD. An outbreak of infectious hepatitis among chimpanzee handlers at a United States Air Force base. Am J Hyg 1961;73:316--28.
8. Provost PJ, Hilleman MR. Propagation of human hepatitis A virus in cell culture in vitro. Proc Soc Exp Biol Med 1979;160:213--21.
9. Alter HJ, Bloomberg BS. Further studies on a "new" human isoprecipitin system (Australian antigen). Blood 1966;27:297--309.
10. Tumpey TM, Basler CF, Aguilar PV, et al. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. Science 2005;310:77--80.
11. Xu R, Ekiert DC, Krause JS, Crowe JE Jr, Wilson IA. Structural basis of preexisting immunity to the 2009 H1N1 pandemic influenza virus. Science 2010;328:357--60.
12. Mock M, Fouet A. Anthrax. Annu Rev Microbiol 2001;55:647--71.
13. Jernigan DB, Raghunathan PL, Bell BP, et al. Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. Emerg Infect Dis 2002;8:1019--28.
14. Hoffmaster AR, Fitzgerald CC, Ribot E, Mayer LW, Popovic T. Molecular subtyping of *Bacillus anthracis* and the 2001 bioterrorism-associated anthrax outbreak, United States. Emerg Infect Dis 2002;8:1111--6.
15. Hoffmaster AR, Ravel J, Rasko DA, et al. Identification of anthrax toxin genes in a *Bacillus cereus* associated with an illness resembling inhalation anthrax. Proc Natl Acad Sci USA 2004;191:8449--54.

16. CDC. Update: multistate outbreak of *Escherichia coli* O157:H7 infections form hamburgers---western United States, 1992--1993. MMWR 1993;42:258--63.
17. Laboratory investigation of a multistate food-borne outbreak of *Escherichia coli* O157:H7 by using pulsed-field gel electrophoresis and phage typing. J Clin Microbiol 1994;32:3013--7.
18. Swaminathan B, Barrett TJ, Hunter SB, Tauxe RV; CDC PulseNet Task Force. PulseNet: the molecular subtyping network for foodborne bacterial disease surveillance, United States. Emerg Infect Dis 2001;7:382--9.
19. CDC. *Escherichia coli* O157:H7 infections associated with eating a nationally distributed commercial brand of frozen ground beef patties and burgers---Colorado, 1997. MMWR 1997;46:777--8.
20. Christensen ML. Human viral gastroenteritis. Clin Microbiol Rev 1989;2:51--89.
21. Fraser DW, Tsai TR, Orenstein W, et al. Legionnaires' disease: description of an epidemic of pneumonia. N Engl J Med 1977;297:1189--97.
22. McDade JE, Shepard CC, Fraser DW, Tsai TR, Redus MA, Dowdle WR. Legionnaires' disease: isolation of a bacterium and demonstration of its role in other respiratory disease. N Engl J Med 1977;297:1197--203.
23. Brenner DJ, Steigerwalt AG, McDade JE. Classification of the Legionnaires' disease bacterium: *Legionella pneumophilia*, genus novum, species nova, of the family *Legionellaceae*, familia nova. Ann Intern Med 1979;90:656--8.
24. Kaufmann AF, McDade JE, Patton CM, et al. Pontiac fever: isolation of the etiologic agent (*Legionella pneumophilia*) and demonstration of its mode of transmission. Am J Epidemiol 1981;114:337--47.
25. Fields BS, Benson RF, Besser RE. *Legionella* and Legionnaires' disease: 25 years of investigation. Clin Microbiol Rev 2002;15:506--26.
26. Xu J, Kochanek KD, Murphy SL, Tejada-Vera B; Division of Vital Statistics. Deaths: final data for 2007. Natl Vital Stat Rep 2010;58:1--72.
27. Rifai N, Cooper GR, Brown WV, et al. *Clinical Chemistry* journal has contributed to process in lipid and lipoprotein testing for fifty years. Clin Chem 2004;50:1861--70.
28. Myers GL, Kimberly MM, Waymack PP, Smith SJ, Cooper GR, Sampson EJ. A reference method laboratory network for cholesterol: a model for standardization and improvement of clinical laboratory measurements. Clin Chem 2000;46:1762--72.
29. Bellinger DC, Bellinger AM. Childhood lead poisoning: the torturous path from science to policy. J Clin Invest 2006;116:853--7.
30. Pirkle JL, Brody DJ, Gunter EW, et al. The decline in blood lead levels in the United States. The National Health and Nutrition Examination Surveys (NHANES). JAMA 1994;272:284--91.
31. Pirkle JL, Kaufmann RB, Brody DJ, Hickman T, Gunter EW, Paschal DC. Exposure of the U.S. population to lead, 1991--1994. Environ Health Perspect 1998;11:745--50.
32. CDC. Blood lead levels---United States, 1999--2002. MMWR 2005;54:513--6.
33. Jones RL, Homa DM, Meyer PA, et al. Trends in blood lead levels and blood lead testing among US children aged 1 to 5 years, 1988--2004. Pediatrics 2009;123:e376--85.
34. Pirkle JL, Flegal KM, Bernert, JT, Brody DJ, Etzel RA, Maurer KR. Exposure of the US population to environmental tobacco smoke: the Third National Health and Nutrition Examination Survey, 1988 to 1991. JAMA 1996;275:1233--40.
35. CDC. Fourth national report on human exposure to environmental chemicals. Available at http://www.cdc.gov/exposurereport/. Accessed August 10, 2010.
36. Temin HM, Mizutani S. RNA-dependent DNA polymerase in virions of Rous sarcoma virus. Nature 1970;226:1211--3.
37. National Center for Biotechnology Information, GenBank statistics. Growth of GenBank (1982--2008). Available at http://www.ncbi.nlm.nih.gov/genbank/genbankstats.html . Accessed August 10, 2010.

38. Mullis K, Faloona F, Scharf S, Saiki R, Horn G, Erlich H. Specific enzymatic amplification of DNA in vitro: the polymerase chain reaction. Cold Spring Harb Symp Quant Biol 1986;51(Pt 1):263--73.
39. Efcavitch JW, Thompson JF. Single-molecule DNA analysis. Annu Rev Anal Chem 2010;3:109--28.
40. Rushing JF, Kumar CV, Gutkind JS, Patel V. Measurement of biomarker proteins for point-of-care early detection and monitoring of cancer. Analyst 2010. Epub 2010.
41. Pan Y, Sonn GA, Sin NL, et al. Electrochemical immunosensor detection of urinary lactoferrin in clinical samples for urinary tract infection diagnosis. Biosens Bioelectron 2010. Epub 2010 Jul 8.

FIGURE 1. Laboratorians reading and checking serologic tests to determine presence of influenza A/NJ/8/76 (swine flu) and registering antibody rise to the swine influenza virus during vaccine testing trials. 1976

Photo: CDC

Alternate Text: Figure is a photo of laboratorians checking serologic tests for swine flu in 1976.

FIGURE 2. Dr. Joseph E. McDade (left), and Dr. Charles C. Shepard, working with a microscope in CDC's leprosy and Rickettsia laboratories in 1977. On January 14, 1977, they isolated the agent that had caused the Legionnaires outbreak

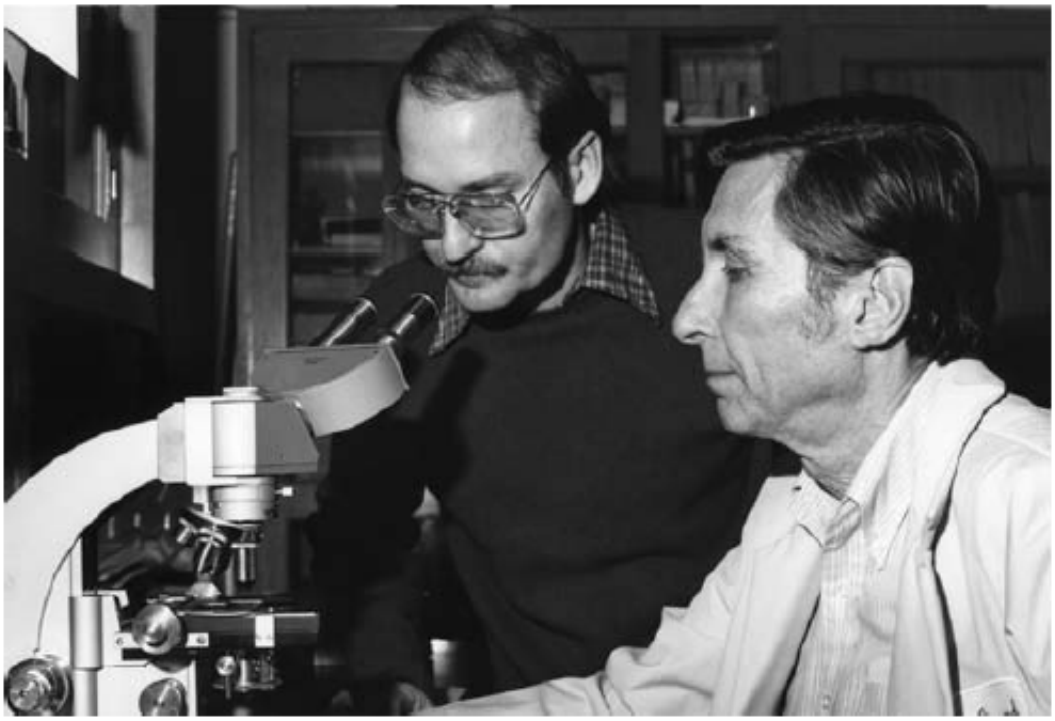

Photo: CDC

Alternate Text: The figure is a photo of Dr. Joseph E. McDade and Dr. Charles C. Shepherd working with a microscope in a CDC lab.

FIGURE 3. A laboratorian using a manual method for conducting a cholesterol determination. 1966

Photo: CDC

Alternate Text: The picture is a photo of a CDC worker in a lab using the manual method for checking a sample for cholesterol in 1966.

is not responsible for the content of pages found at these sites. URL addresses listed in *MMWR* were current as of the date of publication.

All *MMWR* HTML versions of articles are electronic conversions from typeset documents. This conversion might result in character translation or format errors in the HTML version. Users are referred to the electronic PDF version (http://www.cdc.gov/mmwr) and/or the original *MMWR* paper copy for printable versions of official text, figures, and tables. An original paper copy of this issue can be obtained from the Superintendent of Documents, U.S. Government Printing Office (GPO), Washington, DC 20402-9371; telephone: (202) 512-1800. Contact GPO for current prices.

**Questions or messages regarding errors in formatting should be addressed to mmwrq@cdc.gov.

Page last reviewed: October 07, 2011
Page last updated: October 07, 2011
Content source: Centers for Disease Control and Prevention

Centers for Disease Control and Prevention 1600 Clifton Road Atlanta, GA 30329-4027, USA
800-CDC-INFO (800-232-4636) TTY: (888) 232-6348 - Contact CDC–INFO