Postvaccinal Encephalitis

The value of immunization against smallpox, pertussis, and rabies outweighs the occasional serious complications that sometimes result in damage to the central nervous system.

By Joseph Jenkins, M.D.

Immunization procedures are very important in disease prevention. Some of these procedures, although not understood entirely at the time they were first used, originated at the dawn of human history. In our age these methods have long since become established and, by virtue of their success, have acquired an unquestioned right to be included in the medical armamentarium.

Though the value of immunization remains unquestioned, sufficient data have been collected to show clearly the dangers involved in the use of these prophylactic agents. Use of most of the materials results in some local discomfort at the site of application. There may be, for example, the burning that occurs when certain preparations are injected. Local swelling, heat, and tenderness may follow the injection, or there may be soreness for a time of the entire extremity. On occasion a non-tender induration will remain at the injection site for a few days or weeks. Smallpox vaccination is, of course, an actual disease, i.e., vaccinia, whose usual major manifestation occurs only at a local site.

These features of immunization are undesirable but not serious. The post-immunization encephalopathies, however, give cause for concern. Because these complications may lead to death or, what is perhaps worse, an existence with permanent brain damage, studies to clarify the problem have been made. We now know the frequency with which to expect these serious complications, and such knowledge has been helpful in establishing the broad policies of certain immunization programs. Some progress, moreover, has been made in the past few years in alleviating these serious consequences.

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It is the purpose of this paper, then, to discuss the central nervous system injuries that may follow vaccinia and immunization for pertussis and rabies. Data that indicate the value of the procedures will be examined. We shall mention the risks involved, indicate the course and outcome, and comment on certain precautionary measures.

Smallpox

History has attested the importance of immunity to smallpox. The catastrophic epidemics of the New World after the arrival of Columbus and the rush of the disease throughout the North American Indian populations in which millions died have never been seen since Edward Jenner. The continuing importance of adequate smallpox immunization is demonstrated by the Hongkong epidemic of 1937-1938 in which about 2,000 persons died (1); the Glasgow outbreak of 1942 which, although rapidly controlled, killed 24 per cent of those infected (2); the Seattle outbreak in 1946, which produced at least 51 cases with 16 deaths and took four months to stamp out (3).

An opportunity to measure the possible dangers of vaccination arose out of a series of events that began on February 24, 1947 (4). Eugene LeBar, a 47-year-old merchant who had lived in Mexico for six years, started on a bus trip from Mexico City to New York. Apparently in good health when he left Mexico, he was ill by nightfall. He developed a rash on February 26. On March 1 he registered at a hotel in New York City. During the following five days, he did a little sight-seeing and walked through a large department store. On March 5 he entered Bellevue Hospital. His illness progressed rapidly, and on March 10 he died. A post-mortem diagnosis of smallpox was made.

By April 12 there were twelve proved cases of smallpox in the environs of New York City, five in children and seven in adults. Two of these twelve persons died. Of the twelve only three had ever been vaccinated, and three more than forty years previously. An emergency was proclaimed through the press and radio. Within one month 6,350,000 people in New York City were vaccinated, over 5,000,000 within two weeks, following an appeal made by the mayor. There were no more cases of smallpox. These were the events; what, then, were the sequelae of such a large-scale vaccination program?

The sequelae were revealed by June 15, when fifty possible cases of post-vaccinal encephalitis were reported to the Department of Health. Encephalitis was found not to be the diagnosis in four of these cases. Of the remaining forty-six, eight died. There were other sequelae. For example, a 66-year-old man died of septicemia following infection of the vaccination site.

These results had been anticipated by the New York authorities who, even before the campaign was initiated, considered encephalitis as a risk to be encountered following vaccination. But at that time the decision, as to whether or not smallpox was a more serious risk to the city than the complications of vaccinia, had to depend on statistical analysis alone. Information from other sources indicated the vaccinia risk would be small. The risk of death from an unchecked epidemic of smallpox would be far greater. The statistics showed New York City and the United States to have a low immune status for smallpox, lower in fact than most of the civilized countries of the world. Studies of small groups in New York City demonstrated, for example, that susceptibility to smallpox was as high as 93 per cent in a group of students and teachers in New York University. Later studies based on the results of the vaccination campaign in New York City showed that only 26.4 per cent of the population had immune reactions to their vaccinations. To present the data differently, estimates based on epidemics of smallpox occurring in recent years in similar populations in the United States indicated that had not this program been carried out, there would have been 4,310 cases of smallpox with 902 deaths. The figures are in sharp contrast to the 8 deaths among the 46 cases of probable postvaccinal encephalitis that actually occurred. The authorities had no choice but to recommend city-wide vaccination.
Thus we see postvaccinal encephalitis emerging as an important complication of smallpox vaccination. It is interesting to compare the New York experience with other sources as to the incidence of postvaccinal encephalitis. The European incidence has been considerably higher than in this country. The highest reported ratio is that in the Tyrol, one case of postvaccinal encephalitis in 640 vaccinations. The Netherlands have reported one case in 5,000 vaccinations. Scotland reported a ratio of 1:6,600; Sweden, 1:30,000; England, 1:50,000; pre-war Germany, 1:100,000; no cases were reported in Russia, none in Yugoslavia, and none in Rumania. Incidence of encephalitis following vaccination in the New York epidemic was one case to 110,000 vaccinations.

In the New York epidemic none of the cases of encephalitis occurred in an infant. Most authorities agree, however, that encephalitis occurs more commonly in children between the ages of three and twelve years. Although cases in infants do occur, they are rare, probably not more than one in eight million vaccinations. The distribution of cases between the sexes is about equal. The mortality rate in Europe has been high, up to 50 per cent, low in the United States. The New York experience revealed a mortality rate of less than 9 per cent.

The diagnosis of postvaccination encephalitis is difficult. The symptoms are likely to be fairly constant from case to case but are not specific in themselves. The patients will present such symptoms as a sudden onset of fever, headache, vomiting, and disorientation. In the more severe cases, the evidence of mental disturbance is marked—there are symptoms of aphasia, convulsions, stupor, and coma. Signs of intracranial disease are present; that is, one will usually find stiffness of the neck, the pathologic signs of Kernig and Brudzinski, and paralysis of the extremities may occur. The spinal fluid obtained by lumbar puncture will show an increase in cells, the sugar content of the spinal fluid will be normal. Initially these symptoms point to a whole group of diseases such as epidemic meningitis, or tuberculous meningitis, cerebral vascular accidents, lead poisoning, and even tetanus. Many of these can be ruled out when the laboratory evidence is obtained. Even so there is an entire group of diseases referred to as the virus encephalitides, of which eastern and western equine encephalitis and poliomyelitis are members, which may not for some time be eliminated as possible causes of the symptoms presented by these patients.

Severe as postvaccination encephalitis may be, many patients have shown remarkable improvement in two to three days and have been left with no residual damage. Death, however, may occur and hemiparesis, optic atrophy, cortical degeneration, and other neurologic disabilities may result from the disease.

Another serious complication of vaccination took the lives of two infants in the New York epidemic. These two infants, aged four and eight months, suffered from a not uncommon complaint, atopic eczema. They died as a result of a generalized vaccinia acquired by contact with recently vaccinated persons.

During the New York campaign there were 43 cases of vaccinia (varicelliform eruption of Kaposi) (5). Sixteen of these cases were studied at the Kingston Avenue Hospital for contagious diseases. All 16 patients had either a personal or family history of allergy. Atopic eczema was found in all cases. Eleven of these cases occurred in patients under two years of age, all were under seven years of age.

The incubation period averaged ten days following vaccination. By this time the vaccination reaction was well developed, but there were no severe constitutional reactions. Then the patients suddenly experienced high fever, irritability, edema of the face, and intense pruritis, often leading to extensive excoriation of the skin, especially of the face. These symptoms were accompanied by a widespread eruption occurring largely at the sites of the eczema. The lesions were pustular, becoming almost bullous in character. They enlarged, spread, tended to coalesce and, in two days, formed thick dark crusts. The febrile period lasted from five to seven days. In some patients the temperature was sustained at 104° F. for nearly the entire period. When healing occurred the patients were left with scars of smooth depigmented skin resembling typical vaccination scars.

The impression has been gained that these patients can acquire the disease by direct contact with some individual who is experiencing a "take" following vaccination. Others have suggested that nasal droplets, fomites, and urine may also be means of establishing contact. In addition, it seems well established that patients with atopic eczema have skin which is especially susceptible to the vaccinia virus. Moreover, once the vaccinia has become generalized, these patients suffer from severe constitutional symptoms. Emphasis must be placed, then, on the importance of atopic eczema as a contraindication to vaccination and also on the importance of preventing contact of vaccinated persons with children who have atopic eczema.

Pertussis

Innumerable strides have been made in the past 40 years in reducing the number of infant deaths caused by pertussis. Yet even today the mortality rate of hospitalized pertussis patients under one year of age is still 25 per cent. The threat to infant life is unquestioned. It is gratifying to know that so valuable an aid as pertussis vaccine is available. A recent study conducted in Norfolk, Virginia, showed that severe pertussis occurred eight times as frequently in the unvaccinated as in the vaccinated (6).

Since the beginning of whooping cough immunization programs, reactions to the vaccine have been severe enough to cause concern. In April 1948, the evidence of encephalopathy following injection of pertussis vaccine was presented to the medical profession by Byers and Moll (7). Fifteen cases were studied. These were patients admitted to Children's Hospital in Boston, Massachusetts, over a ten-year-old period. Each patient had convulsions beginning a few hours after the injection of prophylactic pertussis vaccine. All were normal children, prior to inoculation, whose ages ranged between five and eighteen months. Twelve of the patients were boys and three were girls; three of the former had a family history of epilepsy, hydrocephalus, or "febrile convulsions."

The history of all these patients showed a sudden onset of severe symptoms referable to the central nervous system, ranging from mild irritability and drowsiness to coma. The outstanding symptom among the group was convulsions which lasted from a few minutes to several days. The onset of these alarming episodes was as early as 20 minutes after inoculation to as late as 72 hours. The acute illness lasted from 36 hours to 10 days. Later studies revealed the degree of brain damage in these cases.

In thirteen of the children, convul-
sions continued to occur over a variable period of time. Of the entire group one child recovered completely, two died after a long illness, five were hemiplegics, and two were to all purposes decerebrate. The condition of three was not evaluated because of the short observation period. Altogether, nine patients out of the fifteen showed a significant degree of cerebral damage.

Reports from other communities do not present similar findings, but other communities have been by no means as carefully studied. Toomey in Cleveland, Ohio, canvassed a large number of physicians in several parts of the country, and 38 cases of possibly similar nature have been uncovered (8). This represents a collective experience based on several hundred thousand injections.

Globus and Kohn from Mount Sinai Hospital, New York, have recently reported two similar cases, the first a nine-month-old boy who, shortly after his second injection of pertussis vaccine, became irritable and drowsy and by the tenth post-injection day suffered repeated convulsions (9). At the time of their report (October 1949), he was making slow improvement. The second patient, aged eight months, also a boy, experienced convulsions and stupor 18 hours after his second injection of pertussis vaccine. The patient's course was severe and steadily downhill. He died on his thirtieth day in the hospital. Postmortem findings were consistent with primary degenerative encephalomyelopathy.

These studies demonstrate that pertussis immunization may be complicated by convulsions and subsequent long-term cerebral damage, but certainly the reactions, as so far reported, are rare. Some even question whether the cases cited can all definitely be attributed to pertussis inoculation. The implications, however, are clear.

It is encouraging that in the past two years the National Institute of Health has developed a toxicity test for pertussis vaccines. It is hoped that this test will eliminate batches of vaccine which may be excessively toxic.

In view of the clear-cut evidence of the damage pertussis can do, particularly among infants, pediatricians as a group do not consider the above data a contraindication to pertussis immunization. In particular, Doctors Byers and Toomey do not recommend withholding inoculation with pertussis vaccine. Until we have a therapeutic agent which will bring about a rapid cure of pertussis, vaccination with its attendant dangers is still the best prophylaxis.

Obviously, exactly the same problem presents itself in the use of pertussis vaccine as had to be considered in the use of vaccinia to provide protection against smallpox. Smallpox can be severe, the mortality rate high; communities which are resistant to vaccination predispose the susceptible groups to devastating epidemics. The case is similar for pertussis, although the frequency of reaction is not nearly so great as with vaccinia. In the face of these unpleasant possibilities, the risk of encephalitis in vaccinia and of central nervous system damage following pertussis vaccination has simply to be accepted. Such incidents, fortunately, are rare.

Rabies

Rabies, a dread disease known since antiquity, was described by Aristotle and given the name hydrophobia by Celsus in the First Century, A.D., because its human victims showed marked aversion to water. It is a disease that is, after a brief and terrifying course, invariably fatal.

By the end of the Nineteenth Century, the Pasteur treatment became a recognized prophylaxis for rabies. This was a method by which the highly virulent "street virus" was modified by repeated passages through rabbits into the "fixed virus" that would regularly bring down fresh rabbits with the disease in a fixed period of about seven days. The spinal cords of these rabbits were then removed and slowly dried at room temperature. By this means a weaker virus was obtained and used for vaccination.

In 1926 the Semple method of preparing vaccine was accepted, and this is the vaccine now most widely used in the U.S. In the Semple method the brains of rabbits infected with the "fixed virus" are treated for 24 hours with phenol and heat to kill the virus. After appropriate tests indicate absence of the living virus, this material is used in a series of 14 injections of 2 cc. each to establish immunity to rabies in the human suspect.

Serious questions concerning rabies vaccination grew rapidly out of experience with it. One of the great authorities in the field, Webster, could not find convincing evidence to support the use of rabies vaccine. Nevertheless, in the same report, he provided data for its use (10).

There can, however, be no doubt as to the reactions derived from the use of vaccine itself in human beings. One source reports over a million treatments. Major reactions occurred in 181 subjects, an incidence of 1 to 5,861; of these 48 were fatal, one fatality in 22,100 treatments. The reactions were more frequent with the Pasteur treatment than with the Semple method.

The major reactions may be of two types. One is the so-called dorsolumbar type in which a reaction in the spinal cord is followed by paralysis. About 5 per cent of this type may be fatal. The second type, Landrys, is again a myelitis but progressively ascends the spinal cord with concurrent paralysis. In about 30 per cent of these the reaction may involve the base of the brain and the patients die.

In a recent study from Los Angeles an attempt was made to evaluate the Semple vaccine reactions (11). Rabies is endemic in this city of three and one-half million people. About 10,000 bites a year are reported, almost all of these by dogs. There must be many more unreported bites. About 70 persons a year are bitten by animals known to be rabid. Since about 10 to 15 per cent of human beings will contract rabies from the bite of a rabid animal, it was estimated that the incidence of rabies would be from 1:1,400 to 1:2,100. However, during the years 1940-1946, nine cases of severe postvaccination reactions, with one death, occurred among 5,500 people receiving the vaccine—an incidence of 1:600. Evidently in Los Angeles the risk of damage to the central nervous system from rabies vaccine is higher than the risk from rabies.

However intriguing these figures may sound, the problem is not so simple. One fact cannot be avoided: once contracted, rabies is 100 per cent fatal. Most physicians believe that treatment is indicated. Indications for use of the vaccine are many and varied, but most physicians agree on the following: (1)
a bite by an animal proved to be rabid, (2) a bite by an animal which has been lost to observation, (3) a bite about the head. Most certainly, however, the high incidence of complications from the use of rabies vaccine contraindicates its indiscriminate use.

It is distressing to note that rabies, except in the New England states, is now on the increase throughout the country. Much interest has been aroused by Johnson's recent review, which calls attention to the spread of rabies among animals (12). There were 2,800 deaths from this disease among cattle alone from 1938 to 1945, and these are only reported cases. Recent evidence has been presented to demonstrate the efficacy of vaccination for animals, not only farm animals but house pets as well. This mode of attack on the disease offers promise for its control in much the same way that smallpox has been controlled in human beings. Obviously, elimination of the animal reservoir would eliminate the disease in man. Johnson's recommendation is for a federal program of publicity, education, and financing. Such a program practiced on a limited scale, as in New York, has clearly proved its practical value, but the program must be continent-wide to be effective.

There is also promise of improvement in another direction. Experiments conducted by Bell to purify the vaccine appear to be nearing completion (13). Since the rabbit brain tissue substance appears to be the offending material, this is being removed by various means. Others have prepared from brains of rabies-infected guinea pig fetuses a vaccine of high potency which does not appear to induce reactions. Several laboratories have accepted the challenge to improve the vaccine. From these we may hope for a practical solution to the problem of rabies vaccine reactions.

Regardless of the statistical data which can be collected pro and con, rabies vaccine will still be used. Edsall points out that

... the experience of years has firmly established the belief, among all who have studied the problem, that anti-rabic vaccination greatly reduced the chances of contracting rabies. ... And despite the fact that rabies is rare, ... the disease is so horrifying to most minds and death from it is so absolutely certain that people continue to demand and physicians to administer the vaccine, with its attendant discomforts and risks, rather than face even a remote prospect of succumbing to rabies. It has little practical bearing on the case that most people think nothing of daily risking death (or, what is sometimes worse, survival) from spinal-cord injury or skull fracture following an automobile accident. Rabies remains a fear-inspiring menace in the mind of man, and will continue to do so whenever the possibility of contracting the disease exists (14).

Other Diseases

Vaccines prepared from bacterial products as well as certain sera, especially horse serum, may produce lesions of the central nervous system. Typhoid vaccine has been reported to produce lesions of the peripheral nerves, spinal cord, and brain. Winkleman and Gotten recorded encephalomyelitis following the use of serum and vaccine. Immunization procedures for influenza have introduced the problem of reaction to the vaccine as an allergic response. This vaccine is made from the chorioallantoic fluid of influenza-infected chick embryos. Two deaths have occurred following its use; later a history of egg sensitivity was found in each of these individuals.

Curphey has reported a death which he considered to be caused by an allergic reaction in a 3½-year-old white girl. One-half cc. of stock vaccine against type A and B influenza was given as a subcutaneous injection. Four hours after the injection the patient complained of pains in the abdomen, chills followed by vomiting, and convulsions. Her temperature was 109°F. There was no history of egg or chicken sensitivity. By six hours after the injection, the child was hospitalized and showed a pronounced cyanosis. Seven hours later she died, failing to respond to antipyretics, oxygen, and epinephrine. During the last five hours of life voluntary respirations had ceased, and artificial respiration was maintained. Certain features of this case were not consistent with a typical allergic reaction. Another authority who studied the case considers this death to be due to a toxic effect of the virus itself. If this is the case, much care will have to be exercised to ensure the proper dosage when using the purified preparations.

Other vaccination procedures, except for local reactions that may occur, are practically without serious complications. BCG, diptheria, tetanus, and typhoid vaccines are used with impunity. The serious complications which in rare cases follow the use of some of these are frequently explained as anaphylaxis. Efforts are now being made in several laboratories, notably by Pillemer at Western Reserve University to produce highly purified products. We can reasonably hope that major reactions to these will be rare.

Nursing Care

The nursing care which these patients require in both the acute and convalescent phases is complex. The patients are usually helpless. Since vomiting, fever, retention of urine or incontinence of urine and feces, convulsions, coma, or cyanosis are such common symptoms, expert care and ingenuity are needed. Just the basic necessities of cleanliness, antipyresis, self-injury protection, and caloric and fluid intake are difficult to maintain. In view of the total lack of any specific therapeutic agent, good nursing care is most important in the treatment of these difficult cases.

References