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In the United States, immunization policy has been to routinely immunize children 1 to 12 years of age and to selectively immunize susceptible women of childbearing age who are not pregnant and who will avoid pregnancy for a three-month period following immunization.[4] The vaccine has been used primarily for preschool children and early elementary school children. Since the adoption of this immunization policy, the incidence of reported rubella in adolescents and young adults has not decreased significantly. In contrast to the prevaccine era when 60% of rubella cases occurred in children below 9 years of age, since 1976, more than 70% of reported cases have been in individuals 15 years of age and older.[5]

The present study found that 15% of sixth grade students are susceptible to rubella. Conversely, 85% show serologic evidence of protection as defined by an HI titer of 1:8 or greater. This finding from an urban community that is well-served medically may be a higher rate of protection than actually exists in areas not served as well. By comparison, a prevaccine survey of Cincinnati school children in 1968 reported a 26% susceptibility rate in sixth grade students and an identical rate for grades 7 through 12.[6] In other studies of the prevaccine era, a range of 10% to 25% susceptibility rate to rubella was observed in adolescents and young adults.[6] The success of the current immunization program in decreasing the occurrence of rubella in very young children may be a factor in allowing unimmunized children to reach adolescence without the immunity of exposure to natural rubella virus.

Of the 469 students who had a documented rubella vaccination, 13.2% had a HI antibody titer of less than 1:8. These students, defined as vaccine failures, accounted for 59% of those susceptible to rubella. Schiff et al,[9] reported a 13.3% vaccine failure rate in a 1972 survey of first grade children. It cannot be determined from the present study whether this represents a failure of initial seroconversion or a loss of antibody over time. When vaccine is administered by a variety of providers the opportunities may be greater for use of an ineffective lot of vaccine, improper storage of vaccine, or improper timing of the vaccine. Horstmann[3] reported that among initial seroconverters, there is a group of responders with low antibody titers of 1:16 or less. From this group she found a 26% loss of detectable serologic evidence of immunity within five years after immunization.

A limitation of any serologic survey is the definition of protection or susceptibility by quantitative antibody response. Vaccine efficacy is really only borne out by response in vivo to exposure to natural virus and may not perfectly correlate with serologic susceptibility. For individuals who have seroconverted, whether from vaccination or natural rubella, but whose titer has declined to less than 1:8, there is evidence to suggest that upon re-infection with rubella, viremia is an unlikely event.[5] Unfortunately, the subgroup of serologically susceptible individuals who so respond to re-infection is not identifiable by practical means, nor is the actual risk of viremia known.

In the previously mentioned survey of first grade children, Schiff et al[9] found a susceptibility rate of 35% in the low socioeconomic group compared to 14.2% and 14.9% in the middle and high income groups, respectively. This is in contrast to our findings. Acknowledging the limitation of free lunch participation as a rather crude socioeconomic indicator, the lower income students in our survey were less susceptible than upper income students, 10.2% vs 16.5%, respectively. This difference may represent an increased opportunity for natural immunity among lower income children, or possibly improved access to health services. It may also represent a study bias in that lower income children are slightly under-represented among participants. Those lower income participants whose parents gave permission may be those most likely to have received immunizations. School records of nonparticipants were reviewed for rubella immunization, but were not complete enough to allow valid comparison.

The finding of a 13.2% susceptibility rate in students with a documented immunization compared to 18.5% in students without documentation emphasizes the importance for physicians, health departments, and schools to insist on adequate documentation of rubella vaccine. State immunization laws need to require documentation of immunizations for students in all grades, not just at school entrance.

Duration of vaccine-induced immunity is a critical factor in determining rubella immunization strategy. In a 7½ year follow-up of rubella vaccinees, Schiff et al[10] reported a downward trend in titers and loss of detectable antibody in a few students who received either HPV-77, DK-12, or Cedenhill vaccine. While current immunization policy has been successful in protecting many children against rubella, a level of protection has not been achieved, particularly in older children and adolescents, that will prevent future outbreaks of rubella. It has been demonstrated that even protection rates as high as 86% will not prevent introduction and spread of rubella virus,[11] making it unlikely that the circulation of wild virus can be prevented by present immunization strategy.

The effect of current immunization practice to shift to adolescence the majority of rubella cases at a time when vaccine-induced immunity may be dwindling causes concern that the potential risk of congenital rubella may actually be increased, although this has not been observed in terms of

reported cases. As a strategy for further reducing the susceptibility rate during the childbearing years, a recommendation for routine primary or booster rubella immunization of preadolescent girls should be considered in addition to the current emphasis on early childhood immunization. Because of their role in recent outbreaks,[12] consideration should be given to immunizing preadolescent boys as well.

In a benefit-cost analysis of rubella immunization policy, Schoenbaum et al[13] projected both economic advantage and greater reduction in congenital rubella through vaccination of girls at age 12 years in comparison to vaccination of children at age 2 years, assuming 80% acceptance of vaccine by the target groups. The strategy of vaccination of children at age 2 years combined with vaccination of girls at age 12 years gave the greatest potential reduction in congenital rubella, but was less advantageous economically than vaccination only at age 12 years.[13] The assumptions and estimates on which this analysis was based may not be accepted by everyone.

The finding of 30% of sixth grade girls having reached menarche is a major obstacle to a recommendation for routine rubella immunization at this grade level. Serologic testing of 30% of girls at this age is impractical and costly, yet immunization of postmenarchal girls raises concern about inadvertant vaccination of possibly pregnant students. Although evidence from a small number of cases suggests that the risk to the fetus of congenital malformation is very small, if any, when rubella vaccine is given during pregnancy,[14] it is not possible at present to dismiss concern about this risk. As an alternative, giving the vaccine at the fourth or fifth grade level would reduce the likelihood of pregnancy being present in a vaccine recipient. The development of arthralgia following rubella immunization has occurred primarily in postpubertal girls and should be an infrequent adverse effect in this age group.

The recent licensing in the United States of RA 27/3 strain of rubella vaccine is another factor in consideration of a change in immunization policy. It has better immunogenicity than previous rubella vaccines,[15] and thus may improve the immune status of future adolescents who receive it in early childhood. Monitoring of the long-range effect of this vaccine on susceptibility during childbearing years as well as study of the actual, as opposed to theoretical, effect of a second rubella immunization in preadolescents are needed to guide decision-making about immunization strategy.

SUMMARY

The finding in the present study of 15% of sixth grade students susceptible to rubella, a rate similar to that of the prevaccine era, indicates the need for additional measures to reduce the risk of congenital rubella syndrome. Adoption of a policy of routine primary or booster rubella immunization of preadolescents should be considered in an effort to enhance protection during the crucial childbearing years. The questions that remain unanswered as to long-term duration of rubella antibodies, the meaning of declining titers, and the risk to the fetus of maternal re-infection with rubella indicate a need for continued serologic monitoring to determine the effectiveness of rubella vaccine and of immunization practice.

ACKNOWLEDGMENTS

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The authors are grateful for the contributions of Pansy Whicker, School Health Coordinator, the school health assistants of Winston-Salem/Forsyth County Schools, the school health nurses of Forsyth County Health Department, and the Virology Laboratory of the North Carolina Division of Health Services.

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Interesting — hints at many of the specifics of immunologic reactions

MEDICAL PROGRESS

Present status of measles and rubella immunization in the United States: A medical progress report

Saul Krugman, M.D.

NEW YORK, N. Y.

EXTRAORDINARY progress as well as anticipated and unanticipated problems have occurred in the wake of the development and licensure of measles and rubella vaccines. This medical progress report will review the present status of the safety and efficacy of these vaccines for the control of measles and rubella.

From the Department of Pediatrics, New York University School of Medicine.

The Willowbrook studies on measles described in this report were conducted in collaboration with Dr. Joan P. Giles.

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Reprint address: 550 First Ave., New York, N. Y. 10016.

MEASLES

The isolation of measles virus by Enders and Peebles,[1] its adaptation to the chick embryo by Milovanović and associates,[2] and its subsequent attenuation by Katz and associates[3] were followed by the development and licensure of 2 measles vaccines in the United States in 1963: live attenuated measles-virus vaccine (Edmonston B type) and formalin-inactivated alum-precipitated vaccine.[4] At the time of licensure it was obvious that febrile reactions caused by live Edmonston B vaccine occurred too often and were too severe to justify routine use of the vaccine as an immunizing agent. Consequently, many physicians preferred to administer the vaccine with a simultaneous inoculation of measles immune globulin. Other physicians chose to use either killed measles vaccine or a combined killed-live measles vaccine regimen. However, by 1967 it was apparent that the immunogenic and

protective effects of inactivated measles vaccine were transient. Moreover, atypical measles with manifestations which were suggestive of delayed hypersensitivity occurred in recipients of killed vaccine when they were exposed to live measles virus months or years later.[5-7] The clinical manifestations of these reactions included high fever, an atypical rash, edema of the extremities, pneumonitis, and occasionally pleural effusion and abdominal pain.

Inactivated measles vaccine is no longer available for use in the United States. Two live further attenuated vaccines* are used extensively in this country. These vaccines, derived from the Edmonston strain, were produced by additional chick cell passages at a lowered temperature. The Schwarz strain vaccine was developed in 1961 and licensed for use in February, 1965. The "Moraten" vaccine was licensed in 1968. These further attenuated vaccines are less reactive and more acceptable than the original Edmonston B vaccine. However, the antibodies which they induce decline more rapidly and persist at a lower level than those observed after natural measles infection or immunization with Edmonston B vaccine.

Six months after the further attenuated vaccine, Schwarz strain, was licensed for use in the United States, an editorial in the *New England Journal of Medicine* expressed concern about the potential long-term efficacy of this preparation.[8] It stated, in part, "In contrast to the antibody plateau resulting from natural measles or Enders' Edmonston B vaccine, a prolonged decline in antihemagglutinating antibody follows Schwarz further attenuated vaccine. . . . The progressive decline in antibody observed during the first 2 years after vaccination with further attenuated vaccine suggests that a qualitative difference in immunogenicity between these vaccines may exist and raises the possibility that if this decline continues at the same rate, resistance to infection will eventually be lost."

This editorial caused unnecessary confusion and uncertainty about the efficacy of further attenuated measles vaccine. Shortly after its publication additional data became available indicating that measles antibodies had persisted for at least 3 years after vaccination with the further attenuated vaccine (Schwarz strain). A subsequent editorial in the same journal stated, "In the light of these more recent findings, physicians and public health officers can be reassured that the currently available licensed measles vaccines, Edmonston B type and further attenuated type, appear to be effective for the prevention of measles."[9]

How does one reconcile this favorable prediction in 1965 with reports in 1969 describing the occurrence of measles in previously immunized children?[10-12] Before commenting on these reports it is important to record the present status of our studies on immunity to measles, which have been in progress since 1960.[13, 14] Our observations have been made in 2 groups: (1) institutionalized children at the Willowbrook State School and (2) home-dwelling children of the East Nassau Health Insurance Plan group. The routine use of measles vaccine for all susceptible children at Willowbrook eradicated the disease in this institution by 1963; no cases have occurred since that time. Consequently, immunized children in this institution have not been exposed to measles during the past 7 years. In contrast, at least 37 per cent of the Health Insurance Plan home-dwelling children have had repeated exposures to measles during the 8 to 8½ year postvaccination period of observation.

Persistence of measles antibody in institutionalized children following natural infection and immunization. Serial samples of serum were obtained from 68 children who had natural measles between 1960 and 1962: 46 children who received live attenuated measles vaccine, Edmonston type, during the period February, 1960, to March, 1962; 40 children who received the Edmonston-type vaccine plus immune serum globulin from

*Commercially available as Liruqen, Pitman-Moore Co., Indianapolis, Ind., and Moraten, Merck Sharp & Dohme, West Point, Pa.

October, 1960, to October, 1961; and 115 children who received further attenuated measles vaccine, Schwarz strain, from November, 1961, to March, 1963. All serum specimens were tested for measles antibody by the highly sensitive hemagglutination-inhibition test described by Norrby.[15]

The results of the 8 to 10 year follow-up are illustrated in Fig. 1. The pattern and persistence of the antibody responses were similar for all 4 groups. The simultaneous administration of gamma globulin and Edmonston-type vaccine was associated with a decrease in the geometric mean antibody levels. The use of Schwarz strain vaccine was also associated with antibody levels which were lower than those observed after natural infection or after Edmonston B vaccine. All children who participated in this study had detectable measles antibody during the 8 to 10 year follow-up period of observation. Only one of 115 children who received Schwarz strain vaccine had no detectable antibody 7 years after vaccination (Fig. 2).

Persistence of measles antibody in home-dwelling children following immunization with live further attenuated measles virus vaccine (Schwarz strain). During an 8½ year follow-up of 210 children, more than 37 per cent of this group were exposed to measles without developing clinical evidence of the disease. All 56 children who were tested at 8½ years had detectable measles hemagglutination-inhibition antibody; the geometric mean titer was 1:60 (Fig. 3).

A comparison of geometric mean antibody titers in the home-dwelling children who had repeated exposures to measles with titers in institutionalized children who were not exposed is shown in Fig. 4. The significantly higher titer at 8 years in home-dwelling children, 1:60, as compared with the lower

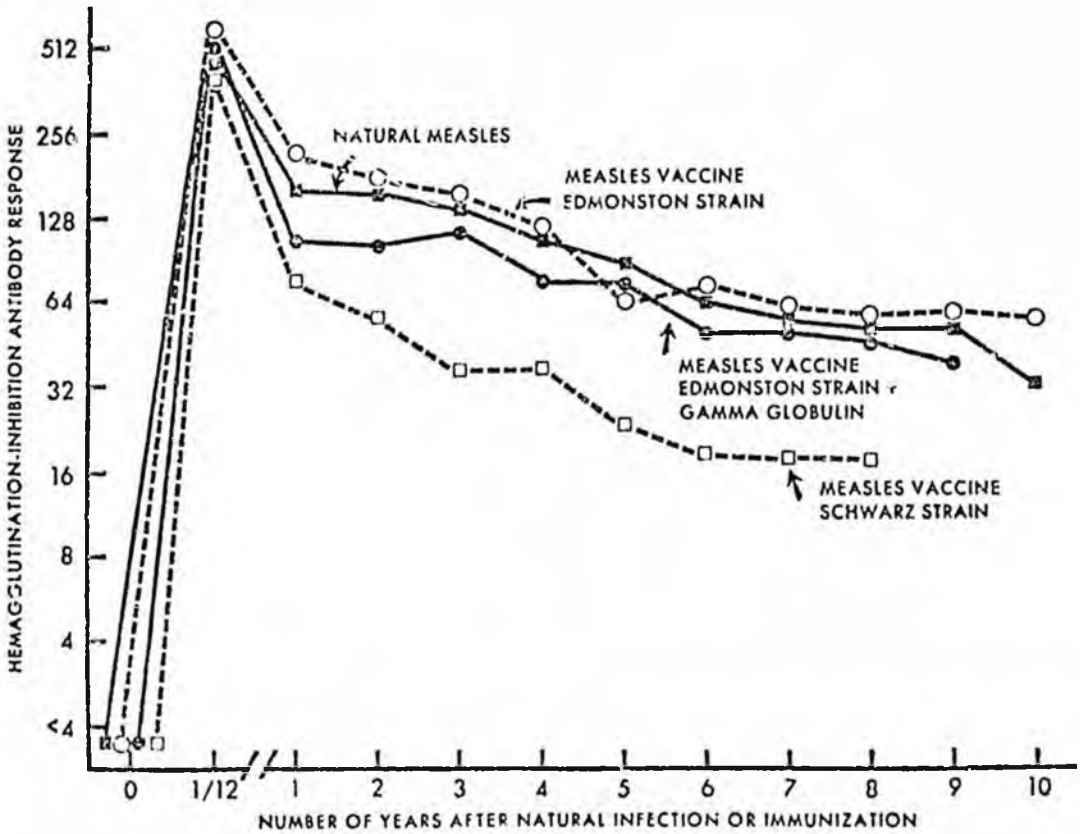

Fig. 1. Geometric mean hemagglutination-inhibition antibody titers following natural measles infection and vaccination with live attenuated measles virus vaccines, (a) Edmonston strain, (b) Edmonston strain plus gamma globulin, and (c) Schwarz strain.

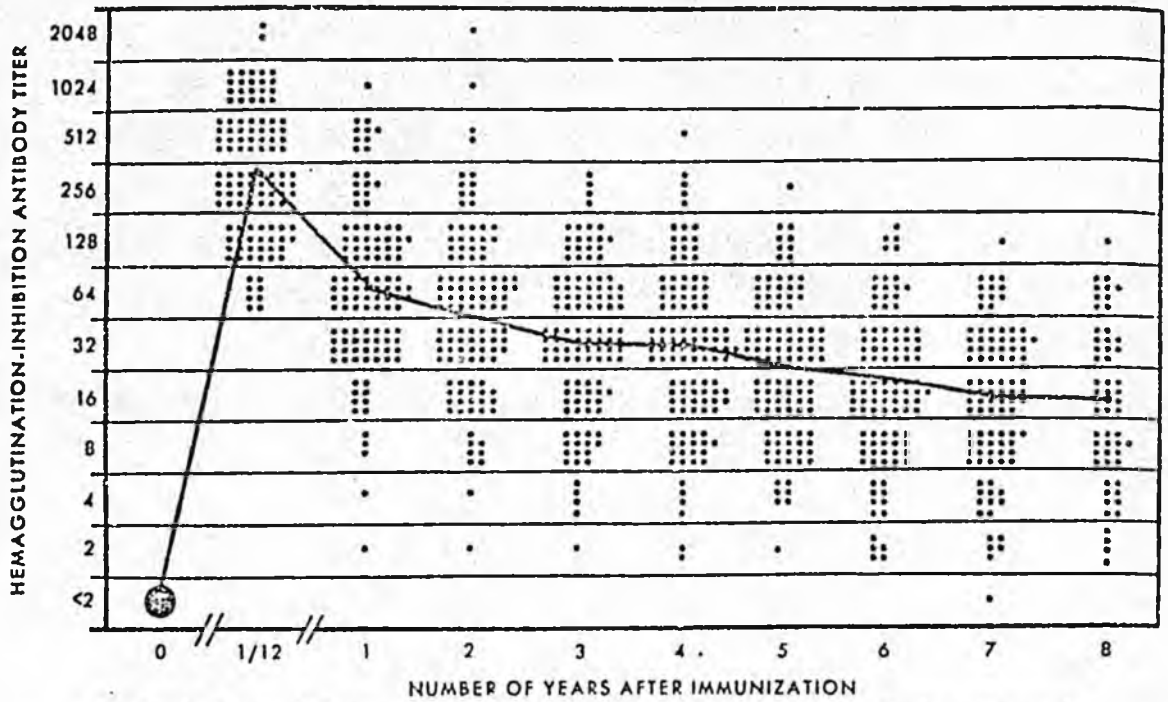

Fig. 2. An 8 year follow-up of institutionalized children who received live further attenuated measles virus vaccine, Schwarz strain. The black dots represent the individual hemagglutination inhibition antibody titers and the solid line represents the geometric mean antibody titer.

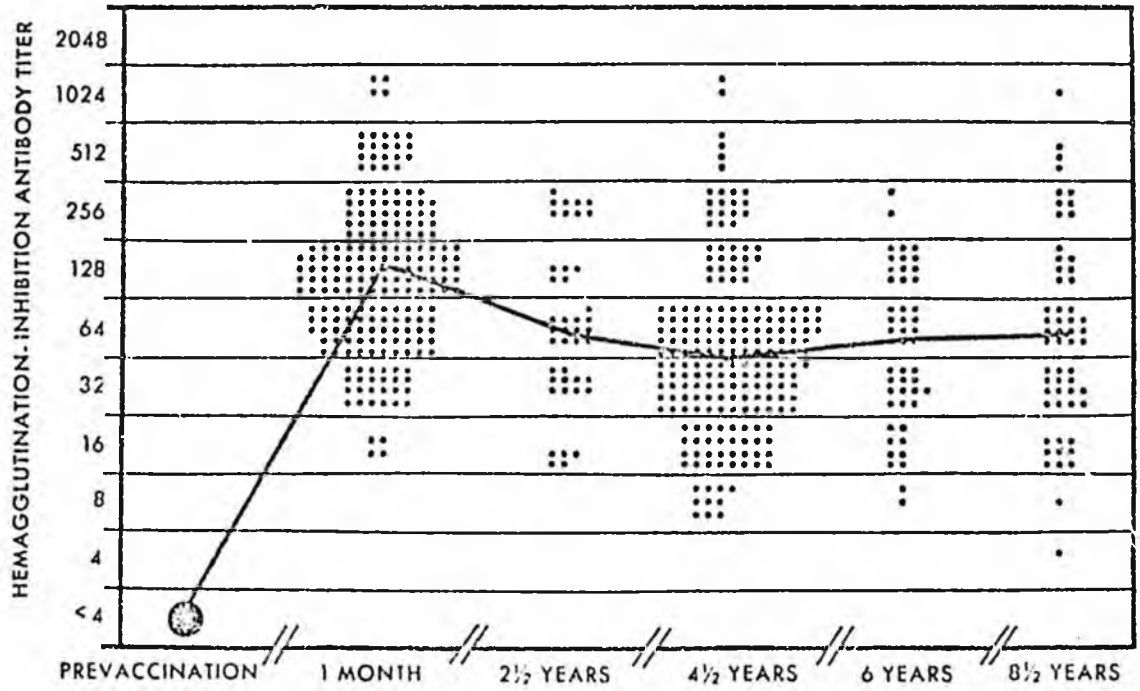

Fig. 3. An 8½ year follow-up of home-dwelling children who received live attenuated measles vaccine, Schwarz strain, and 0.2 ml. of gamma globulin. These children had repeated exposures to measles, unlike the institutionalized children (Fig. 2) who had no exposure.

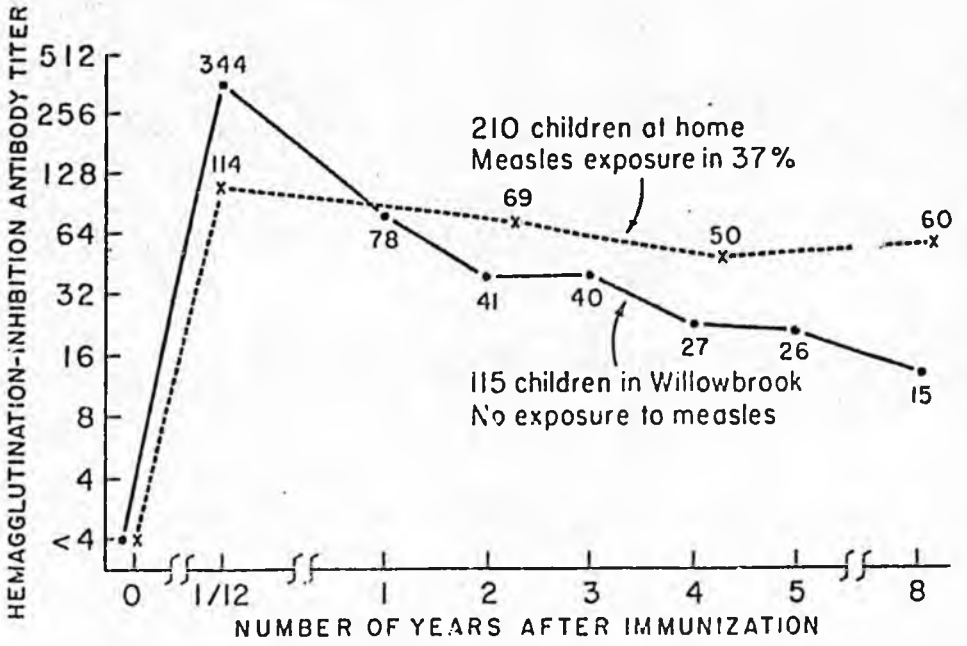

Fig. 4. Comparative geometric mean antibody titers of the institutionalized and home-dwelling children depicted in Figs. 2 and 3.

titer of 1:15 in the institutionalized children probably reflects a booster response associated with reinfection following exposure to wild measles virus. In spite of repeated exposures to measles, the Health Insurance Plan children were solidly protected against the clinical disease.

The typical antibody response following primary infection of 10 children with live attenuated measles virus is shown in Fig. 5. Hemagglutination-inhibition antibody was first detectable on the tenth day, and peak levels were observed by the twenty-seventh day. In contrast, reinfection of 25 previously immunized children was characterized by an initial rise of hemagglutination-inhibition antibody on the first day; peak levels were observed as early as the twelfth day. The phenomenon of reinfection with booster response has been seen typically in children with low hemagglutination-inhibition antibody titers (less than 1:64); it has not usually been observed in the presence of relatively high antibody titers (exceeding 1:128).

The available evidence indicates that following the priming that occurs with the initial measles virus infection, any subsequent reinfection will be characterized by a booster type of antibody response. Panum, in his classic description of the epidemic of measles in the Faroe Islands in 1846, observed that all old people who had measles in the previous epidemic in 1781 were protected against the disease in spite of lack of exposure during the intervening period of 65 years. This experience demonstrated that repeated exposure was not an essential prerequisite for permanent immunity to measles.

Our longitudinal studies on immunity to measles have provided evidence to support the prediction that live vaccine-induced immunity will be just as protective against clinical measles as naturally acquired immunity. We have never seen a case of measles in a child who was shown to have an antibody response following immunization with live measles vaccine.

Measles in previously immunized children. The reported cases of "measles in previously immunized children" probably represent failure to achieve a primary live vaccine-virus infection because of one or more of the following factors: (1) Administration of vac-

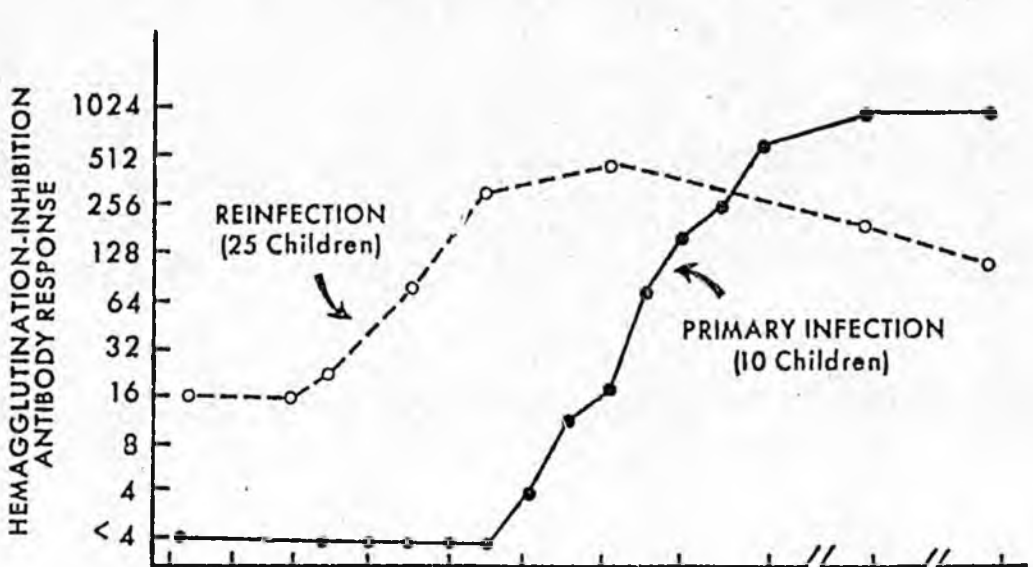

Fig. 5. Pattern of hemagglutination-inhibition antibody response following primary infection and reinfection with live attenuated measles vaccine. The hemagglutination-inhibition antibody titers represent mean levels of 10 children with primary infection and 25 with reinfection. Note booster response associated with reinfection.

cine before 12 months of age when maternal measles antibody may have been present. Suppression of the antibody response is most apt to occur when measles immune globulin is given with the vaccine to an infant with residual transplacentally acquired antibody. (2) Administration of vaccine virus which may have been inactivated by inadequate refrigeration, by excessive exposure to light, by use of the wrong diluent containing a potentially virucidal preservative, or by unknown factors. Currently licensed live measles vaccines have been characterized by a seroconversion rate of approximately 98 per cent. Consequently, it is reasonable to anticipate a 2 per cent attack rate in children who were inoculated but not immunized with measles vaccine.

The effect of age on the antibody response of children to live attenuated measles vaccine (Edmonston B with immune serum globulin) is shown in Table I. Among infants 9 to 11 months of age, 86 per cent had a hemagglutination-inhibition antibody response. In contrast, the seroconversion rate in children who received vaccine after 12 months of age was 97 per cent. This study highlights the importance of following the current recommendations of the American Academy of Pediatrics Committee on Infectious Diseases: "In general live measles vaccine should be administered at about 12 months of age or shortly thereafter." In certain developing countries and in certain epidemic situations it may be wise to immunize infants between 6 and 12 months of age. However, under such circumstances a second inoculation of vaccine should be given after 12 months of age to protect infants who failed to respond to the first inoculation.

Table I. Measles hemagglutination-inhibition antibody response in infants and children who received live attenuated measles virus vaccine, Edmonston Type, plus gamma globulin

Age group (months)	*No. of children vaccinated*	*Hemagglutination-inhibition antibody response*	
		No.	*Per cent*
9-11	123	106	86
12 or more	899	872	97

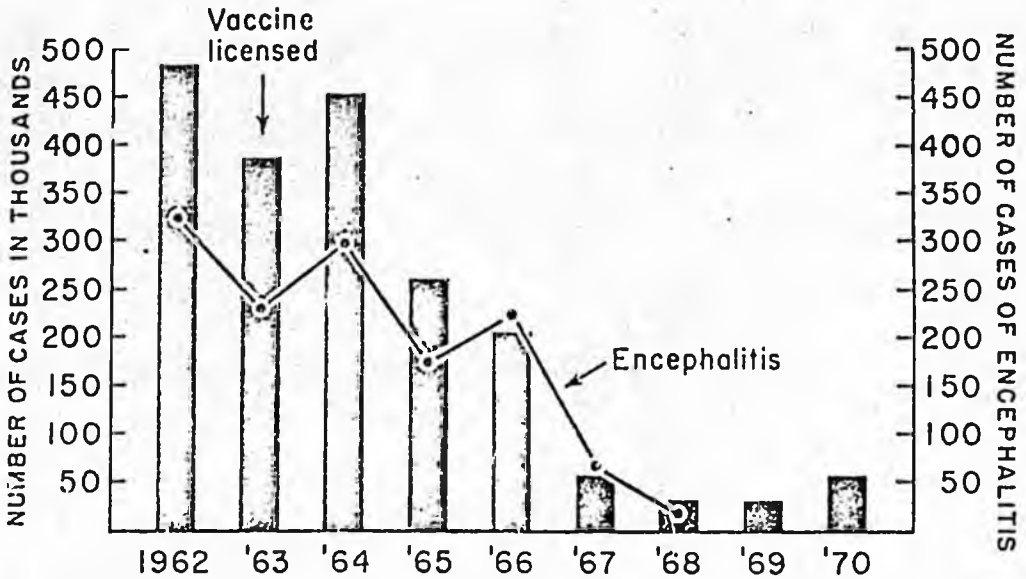

Fig. 6. Reported cases of measles and measles encephalitis in the United States from 1962 to 1970.

The causes of vaccine failure have varied during the reported outbreaks.[10-12] The Governor's Island report[10] identified 73 cases of measles of which 11 (15 per cent) were in previously immunized children and 62 (85 per cent) in those who were unimmunized. However, the attack rate was 2.4 per cent in previously immunized children and 33.5 per cent in unimmunized children; over-all vaccine efficacy was 92.7 per cent. The report from Florida[11] highlighted the occurrence of measles in 18 children who received live measles vaccine and immune serum globulin before they were 12 months of age. The Ohio report[12] involved 14 previously immunized children and 46 who were not vaccinated. The attack rate in the unimmunized group was 52.4 per cent, whereas that of children immunized by the local health department was 1.2 per cent; vaccine efficacy was 99 per cent. However, 17.9 per cent of the children previously inoculated by one private physician in the same city developed measles, a vaccine efficacy of only [illegible] per cent. The measles vaccine in this physician's office was exposed to temperatures which may have caused a decrease in vaccine potency.

Present status of live measles vaccine. Prior to licensure of live attenuated measles vaccine in March, 1963, approximately 500,000 cases of measles and 300 to 400 cases of encephalitis were reported in the United States each year. The extensive use of vaccine has been followed by a dramatic decline in the incidence of measles and encephalitis (Fig. 6). An all time low was reached in 1968 and 1969 when approximately 25,000 cases were reported, a decreased incidence of 95 per cent. The rising incidence of measles in 1970 has not been related to vaccine efficacy but rather to a failure of delivery of health care to infants and children from various poverty areas. The occurrence of measles in previously immunized children is not a result of waning immunity.

The dramatic decline in the incidence of measles encephalitis has been very reassuring. It is obvious that the risk of encephalitis following natural measles infection, approximately one per 1,000 cases, is significantly greater than the risk of vaccine-associated encephalitis, estimated to be about one per one million vaccinees. The incidence of encephalitis of unknown etiology in the United States in 1968 was 1.2 cases per one million children, one to 9 years of age.[10] It seems clear that postvaccination encephalitis has not been an important problem.

The association of subacute sclerosing panencephalitis with natural measles has been well documented.[17] This late neurologic sequela of measles is very rare. It will be difficult to assess the risk of subacute sclerosing panencephalitis without knowledge of the immune status of a child prior to vaccination. During the course of our studies we detected serologic evidence of immunity to measles in approximately 15 per cent of children, 3 to 8 years of age, in spite of the fact that their parents denied a prior history of measles.[18] The extensive use of live measles vaccine during the past 7 years has not been associated with an apparent increased incidence of subacute sclerosing panencephalitis.

Conclusion. At the present time 2 safe, potent, and highly effective live measles vaccines are licensed for use in the United States.* The control of measles will depend on the appropriate use of these vaccines. It will be essential to include the oncoming as well as the present generation of susceptible infants and children in routine immunization programs.

A single dose of vaccine should provide long-term immunity against measles for approximately 98 per cent of inoculated children. The available evidence indicates that reinfection of persons with low levels of antibody has no clinical significance. The booster response induced by reinfection has not been associated with clinical manifestations of the disease.

Measles will continue to occur among the small group of children (approximately 2 per cent) who may be at risk because of failure to respond to an inoculation of vaccine. The solution to this problem is complex. It would be difficult to condone the routine use of a second dose of vaccine because 98 per cent of children are likely to be protected by one inoculation. Many millions of dollars would be wasted each year for the unnecessary vaccination of immune children. It would be more appropriate to use these funds for the solution of other critical health problems.

*Lingen and Moraten. Lingen is the trade name for live further attenuated Schwarz strain vaccine, a product of the Pitman-Moore Co., Zionsville, Ind. Moraten is the trade name of more attenuated Enders' Edmonston virus, a product of Merck Sharp & Dohme, West Point, Pa.

RUBELLA

The extensive epidemic of rubella in the United States in 1964 and its serious consequences have been well documented.[19] The epidemic was responsible for the death and disability of many thousands of infants and for the anguish and despair of their parents. The cost in terms of hospitalization, medical care, rehabilitation, and special education for the multihandicapped survivors has been estimated to exceed 2 billion dollars. This devastating experience highlighted the need for an effective vaccine as the most logical solution of the rubella problem. The extraordinary progress toward this goal was revealed at the International Conference on Rubella Immunization which was held February 18 to 20, 1969.[20]

The development of live attenuated rubella virus vaccine has been remarkably similar to the experience with live measles vaccine. However, the time interval between isolation of virus,[21-22] subsequent attenuation,[23] and licensure in 1969 was 7 years for rubella as compared with a 9 year period for measles. The use of the vaccine has also been accelerated; more than 19 million doses of rubella vaccine as compared with 3.5 million doses of measles vaccine had been given within approximately one year after licensure.

The proceedings of the International Conference on Rubella Immunization provided a comprehensive report of various phases of rubella immunization.[20] The data presented provided the basis for a prelicensing statement on rubella vaccine prepared by the Advisory Committee on Immunization Practices of the Public Health Service and the Committee on Infectious Diseases of the American Academy of Pediatrics.[24] The 2 committees recommended the use of the vaccine for girls and boys between one and 12 years of age, emphasizing that young school children deserve the highest priority because

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they are the major source of virus dissemination in the community. The vaccine was not recommended for pregnant or potentially pregnant women because of the possible risk of fetal infection with the vaccine virus. The committees stated that women of childbearing age should be considered for vaccination on an "individual" basis, if the possibility of pregnancy in the following 2 months could be avoided. Ideally, the immune status of a woman should be determined by performing a rubella hemagglutination-inhibition test. Susceptible women on an effective contraceptive regimen would be good candidates for rubella immunization. The immediate postpartum period would be an excellent time to vaccinate susceptible women.

The goal of the current large-scale immunization program for children is to prevent congenital rubella by providing indirect protection for mothers of rubella-susceptible children and providing girls with immunity to rubella which, hopefully like the natural disease, may be long lasting.

The first goal is the immediate protection of susceptible women if an epidemic of rubella occurs in 1971 or 1972. Rubella epidemics in the United States generally recur at 6 to 9 year cycles; the last one occurred in 1964. The most likely sources of infection of susceptible pregnant women are their own rubella-infected children. Consequently, the immunization of all children in a household should provide indirect protection for their susceptible mothers of childbearing age. In addition, immunization of school children should protect their susceptible teachers. The extensive use of rubella vaccine in 1970 should have a significant effect on the incidence of rubella in communities which have participated in the program. It will be interesting to compare the results of well-immunized and poorly immunized communities.

The second goal of the rubella immunization program in the United States is based on the premise that a primary infection with attenuated rubella vaccine virus will have the same immunologic consequences as a primary infection with wild rubella virus. As indicated in the section on measles, the question of duration of immunity following the use of live further attenuated Schwarz strain vaccine, which was a cause for concern in 1965, is no longer considered a problem. The questions about rubella will be answered by the accumulation of data from studies designed to evalaute the significance of reinfection and the related potential problems of communicability and duration of immunity. The results of these studies on rubella vaccine-induced and natural immunity may or may not reveal quantitative differences which do not apparently exist with measles.

It is well known that the phenomenon of reinfection is a characteristic of rubella as it is of measles.[13, 25-29] Consequently, 2 crucial questions must be answered: (1) Is a reinfected, previously vaccinated, or naturally immune individual contagious? (2) Is there a risk of viremia in a reinfected individual? Answers to these questions will be derived from knowledge of the immunity following naturally acquired infection, vaccination, and rubella reinfection.

Primary rubella infection—naturally acquired. Studies on the natural history of rubella have elucidated the virologic and serologic events of the primary infection.[30] → tonsil area?
Rubella virus is present in the pharynx and blood approximately one week before onset of rash; it may persist for 2 weeks and in rare instances as late as 3 weeks after onset of rash. Viremia, which occurs about one week before onset of rash, is no longer detectable by the second or third day of the exanthem. Antibodies are first detectable shortly after onset of rash, reaching a peak approximately one month later. Recent studies have shown that the pattern and persistence of antibody following natural rubella were similar to those following measles.[31] A 5 year follow-up of 223 women who had rubella during the 1964 epidemic indicated that the rubella hemagglutination-inhibition antibody titers ranged between a low of 1:8 and a high of 1:2,048 or greater. As indicated in Table I, 5 years after natural

→ presence of virus in blood of host

→ symptomatic eruption of sores during course of disease

measles the antibody titers ranged between a low of 1:8 and a high of 1:1,024.

Studies by Davis and associates[28] have provided the quantitative data needed to clarify the problem of communicability. Significantly larger amounts of virus are present in the pharynx and blood of patients during the prerash period of natural rubella. The amount of virus decreases 100-fold to 1,000-fold by the third to fifth day after onset of rash. This finding supports the epidemiologic observation that patients with rubella are most contagious before onset of rash and are rarely contagious after the third day of rash. These virologic and serologic events are essentially the same in subclinical rubella infection (rubella without rash).

An extraordinary study of an epidemic of measles in Greenland in 1962 may contribute to a better understanding of the communicability of rubella. A correlation between time of exposure and communicability was observed during this epidemic.[32] It was obvious that the available health facilities would be inadequate to cope with the problems associated with a major outbreak. Accordingly, it was decided that a "guided epidemic" would be the best solution for a potentially critical situation. The area was divided into 3 quarantinable units: the 800 inhabitants of the town of Umanak, the 500 inhabitants of the 4 most remote settlements, and the 700 inhabitants of the 5 nearest settlements. The plan involved the deliberate exposure of large groups of susceptible individuals to a person or persons with measles; half of the adults and half of the children in each household were asked to volunteer for "artificial infection."

The results of this unique plan were very interesting. Approximately 400 persons visited a patient named Josef on the *first* day of his measles rash. Josef coughed twice in the face of each person! In spite of this exposure, the large number of contacts did not develop measles. Consequently, 3½ weeks later the procedure was repeated but this time patients in the catarrhal, prerash stage of measles were chosen as the source of infection. Under these circumstances the disease was successfully transmitted to the susceptible contacts.

It is well known that measles virus is present in the nasopharynx during the first day of rash, as well as during the catarrhal period of the disease. The failure to transmit the infection on that day was probably a reflection of the minimal quantity of virus present at that time. Although a culture of the throat may have been positive, the amount of virus may not have been adequate to initiate infection. The larger quantities of virus present during the catarrhal period were undoubtedly responsible for the communicability of the disease.

An evaluation of the various epidemiologic and experimental studies on rubella as well as measles suggests that a positive throat culture is not necessarily an indication of communicability. The dose or quantity of virus delivered appears to be the major factor.

Primary rubella infection—vaccine induced. The natural history of primary infection following inoculation of live attenuated rubella virus was well documented in various reports published in the proceedings of the International Conference on Rubella Immunization[20] and in a more recent report by Davis and associates.[28] Similarities and differences have been observed in vaccine-induced infections as compared with natural rubella infections in regard to clinical reactions, virus shedding, antibody response, and communicability.

Clinical reactions. The typical lymphadenopathy and 3 day rash of natural rubella are rarely seen following vaccination; fever is even less common. On the other hand, transient arthritis and arthralgia may occur as frequently after vaccination as it does after natural rubella. It is difficult to compare the relative frequencies of vaccine-associated and rubella-associated joint manifestations because the extensive prospective observations during vaccine trials provided data which could not be obtained under the conditions of epidemic or endemic rubella in the community.

Prior to the licensure of rubella vaccine

it was obvious that transient joint manifestations occurred in 25 to 40 per cent of women and in 1 to 2 per cent of children[33, 34] and that arthritis and arthralgia were milder in susceptible women who received the Cendehill strain as compared with those who received the HPV-77 strain in dog kidney. The extensive experience since licensure of the HPV-77 strain has revealed an increased incidence of joint manifestations in children who received the HPV-77 strain in dog kidney cell culture (Rubella Virus Vaccine, Philips Roxane Laboratories, Inc., Columbus Ohio) as compared with those who received HPV-77 in duck embryo cell culture (Meruvax, Merck Sharp & Dohme, West Point, Pa.). As yet, comparative data are not available following extensive use of the Cendehill strain in rabbit kidney cell culture (Cendevax, Smith, Kline and French Laboratories, Philadelphia, Pa.), because this vaccine was licensed later.

Under the conditions of normal pediatric or general practice a 1 to 2 per cent incidence of transient arthritis and arthralgia would be a relatively unimportant event. On the other hand, the administration of 100,000 doses of vaccine to children in the same community at about the same time could be associated with a pseudoepidemic of 1,000 to 2,000 cases of painful joints. The problem could be compounded because the incidence of joint manifestations in children receiving dog kidney vaccine is approximately 5 per cent or more. In addition, in spite of adequate briefing in package inserts, newsletters, articles in medical journals, and a special letter to all physicians from the Public Health Service, many practitioners were not aware of the well-known phenomenon of benign, transient rubella arthritis. Consequently, many children were admitted to hospitals for study to rule out a diagnosis of rheumatic fever or rheumatoid arthritis, an exercise which caused unnecessary anxiety and expense.

Virus shedding. The appearance of vaccine virus in the pharynx is a phenomenon associated with all of the licensed vaccines. It is clear that attenuated virus is shed for a briefer period of time and in much smaller amounts than wild rubella virus. Meyer and associates[35] have reported that virus-positive throat swabs from vaccinated children contain 100 times less virus than similar swabs from children with natural rubella. Moreover, the attenuated virus has lost much of its capacity to induce an infection by the respiratory route.

Viremia, which is so easily detectable during natural rubella, has been difficult to detect in vaccine-induced infection. Viremia, if present, must be a transient phenomenon characterized by minimal quantities of virus.

Antibody response. Antibody levels following vaccination are significantly lower than those associated with natural rubella. Moreover, there is a delay in the appearance of antibody with increasing attenuation of rubella virus.[20] We consistently detected hemagglutination-inhibition antibody 14 to 17 days after primary infection with wild rubella virus. In contrast, hemagglutination-inhibition antibody following vaccination was usually detected a week or more later, reaching peak levels 6 to 8 weeks after vaccination. In general, antibody levels following vaccination were fourfold to eightfold lower than those observed after natural rubella. This finding was similar to our experience with further attenuated Schwarz strain measles vaccine and natural measles (Fig. 5). It is clear that a definitive answer to the question of persistence of antibody and duration of immunity following rubella vaccination must await the results of surveillance studies.

Communicability. In spite of rare isolated reports which suggest the possibility of communicability,[25, 36] the overwhelming evidence indicates that vaccinated virus-shedding individuals are not contagious. In our experience the attenuated rubella vaccine was not communicable under the same conditions in which we observed a 90 per cent attack rate in susceptible children who were exposed to wild rubella virus.[37] A recent report by Scott and Byrne[38] demonstrated the lack of communicability of the vaccine virus when susceptible pregnant women were ex-

posed to their vaccinated children. Examination of serum specimens obtained before and after exposure revealed no serologic evidence of infection. The available evidence indicates that the potential risk of communicability is negligible. Consequently, there is no contraindication for the use of vaccine in community programs involving children whose mothers are pregnant.

Reinfection rubella. The available evidence indicates that reinfection may occur in persons who have had natural rubella or rubella vaccine. Recent reports by Horstmann and associates[27] and Davis and associates[28] indicated that reinfection was more common in previously vaccinated individuals than in those who had had natural rubella. Evidence of a booster response following exposure to rubella was observed in 80 per cent of previously vaccinated individuals as compared with less than 10 per cent of those who had had natural rubella.[27] Similar observations were reported earlier by Wilkins and associates[25] and Schiff and associates,[26] when they challenged previously vaccinated persons with a relatively unattenuated strain of rubella virus. In most studies there has been a significant correlation between the level of rubella hemagglutination-inhibition antibody and the probability of reinfection. Persons with low levels of antibody were more likely to be reinfected.

Reinfection has been characterized by a fourfold or greater rise in hemagglutination-inhibition antibody and, occasionally, by the presence of small amounts of virus in the pharynx for a brief period of time as compared with primary rubella infection. Viremia has not been detected during the course of reinfection. It is logical, therefore, to assume that the potential risk of fetal infection during reinfection may be negligible or nonexistent. The final answer to this crucial question will come from data accumulated from studies similar to those described by Boue and associates.[29] They are observing 3 women who were immune prior to their exposure to rubella during the early weeks of pregnancy. Sucrose density gradient studies revealed that the specific rise of rubella hemagglutination-inhibition antibody in the 3 pregnant women was IgG, a response characteristic of reinfection rather than primary infection. Even if none of the 3 infants have clinical, virologic, or serologic evidence of congenital rubella at birth, it will be essential to have additional evidence before a final judgment is made, since not all infants are infected as a result of maternal primary rubella infection during the first trimester of pregnancy.

During the early course of our studies on the natural history of rubella,[30] we had an opportunity to obtain serial samples of blood from patients with primary rubella infection and from others who were reinfected with wild rubella virus. The results of serial hemagglutination-inhibition antibody studies in 8 children with primary infection and 5 children with reinfection are shown in Table II. Antibody following primary rubella infection was detectable by the fourteenth to seventeenth day after exposure. Evidence of a booster response following reinfection was observed one week earlier, by the seventh to eleventh day after exposure. The initial response to the primary infection was specific rubella IgM, followed several days later by IgG. In contrast, the booster response consisted of IgG antibody exclusively. Viremia and pharyngeal rubella virus, which were detected during primary infection, were not detected during reinfection.

Rubella reinfection could prove to be a blessing rather than a problem. A primary infection with wild or attenuated rubella virus, like wild or attenuated measles virus, may "sensitize" or prime a person for life. Subsequent exposure to the virus at a time when humoral antibody may be low or nondetectable may be followed by minimal local multiplication of virus which in turn may provoke a prompt boost of antibody, thereby preventing the occurrence of viremia. These immunologic events may inhibit virus multiplication, thereby eliminating the potential problem of communicability.

Conclusion. The potential problems associated with the rubella vaccination program

Table II. Serial hemagglutination-inhibition antibody titers following primary natural rubella infection and reinfection

	No. of days after exposure to rubella virus														
Titer	*0*	*3*	*4*	*5*	*7*	*8*	*10*	*11*	*12*	*13*	*14*	*15*	*17*	*21*	*28*
Primary infection															
Coo	< 8	< 8	—	< 8	< 8	—	< 8	< 8	< 8	—	64	—	128	128	512
Sul	< 8	< 8	—	< 8	< 8	—	< 8	< 8	< 8	—	< 8	—	32	1,024	—
McO	< 8	< 8	—	< 8	< 8	—	< 8	< 8	< 8	—	< 8	—	64	128	128
Vas	< 8	—	—	< 8	< 8	—	< 8	< 8	< 8	—	256	—	1,024	4,096	4,096
Ren	< 8	< 8	—	< 8	[illegible]	—	< 8	< 8	< 8	—	< 8	—	32	4,096	—
Dan	< 8	< 8	< 8	—	< 8	—	< 8	—	< 8	—	< 8	—	32	—	64
Mil	< 8	< 8	< 8	—	< 8	—	< 8	—	< 8	—	< 8	—	16	32	256
Spe	< 8	< 8	< 8	—	< 8	—	< 8	—	< 8	—	8	—	128	--	4,096
Reinfection															
Ber	64	—	—	—	—	256	—	512	—	128	—	128	—	—	—
Lan	256	—	—	—	—	256		1,024	—	—	—	1,024	—	—	512
Pan	128	128	128	—	128	—	2,048		1,024	—	—	256	—	—	256
Her	128	256	—	—	4,096	—	4,096	—	512	—	512	—	—	—	512
Bax	512	512	—	—	512	—	4,096	4,096	—	—	—	512	—	—	1,024

Underlined numbers indicate first evidence of detectable antibody following primary infection and first evidence of booster response after reinfection. Results are recorded as the reciprocal of the rubella hemagglutination-inhibition antibody titer.

in the United States were carefully reviewed in an excellent editorial by Dr. John F. Enders.[40] He presented a fair and objective evaluation of the possible significance of reinfection, potential communicability of the vaccine virus, and duration of immunity. In the concluding paragraph of his editorial he stated, "Accumulating doubts such as these of the long-range effectiveness of the rubella vaccination program should not be allowed for the present to interfere with its continuation." It was regrettable, however, that Dr. Enders' comments were reported out of context by several newspapers. The most blatant distortion of the editorial appeared in a bold headline of the highly respected *New York Times* on August 4, 1970, stating, "Virologist suspects harm in rubella vaccine but would continue its use." During the first week of August, 1970, the combined efforts of all the communications media--newspapers, radio, television, and later, magazines--created a new rubella problem which caused unnecessary anxiety and confusion for physicians and parents who were participating actively in the rubella immunization program. The distorted reports were also transmitted to many other countries.

At the present time 3 safe, immunogenic, well-tolerated, attenuated rubella vaccines are licensed for use in the United States, the HPV-77 strain in duck embryo cell culture, the HPV-77 strain in dog kidney cell culture, and the Cendehill strain in rabbit kidney cell culture. In the wake of extensive large-scale studies, it became apparent that the HPV-77 strain in dog kidney cell culture was not acceptable for routine use in large-scale public health programs involving children; it caused joint manifestations which were significantly more frequent, more severe, and more prolonged than those observed with the other 2 vaccines. The RA 27/3 strain of attenuated rubella vaccine, developed by Plotkin and associates[41] and described at the International Conference on Rubella Immunization, has not been discussed because it has not yet been licensed for use in the United States.

In my opinion the current recommendations for the use of live attenuated rubella vaccine in the United States represent the most logical and most feasible approach for the solution of the rubella problem in this country. Additional experience gained from current and future studies should provide advisory committees with data which may be used as a basis for modifications of the present vaccination program. The recommendations for the use of measles vaccine have been modified on several occasions during the past 7 years. New information which will become available will dictate the need for continuation or modification of current recommendations for the use of rubella vaccine in the United States.

The aim of the present rubella immunization program in Great Britain is to concentrate their efforts on 2 groups: all girls between the ages of 10 and 14 years and susceptible women of childbearing age who have no detectable rubella hemagglutination-inhibition antibody. They realize that this program is not likely to have much effect if an epidemic were to occur within the next few years. On the other hand, they believe that their program may have theoretical advantages for long-term protection against congenital rubella.

In contrast, the immediate aim of the rubella program in the United States is twofold: to routinely immunize girls and boys, one to 12 years of age, the major disseminators of wild rubella virus, and to immunize *susceptible* women of childbearing age on an individual and selective basis. If the immunity does not prove to be durable, it may be appropriate to recommend a second inoculation of vaccine for all girls, who were vaccinated in infancy or early childhood, when they reach the age of 12 years.

The problems associated with the vaccination of women of childbearing age have been aggravated by the failure of many physicians to abide by the following recommendations of the Public Health Service and American Academy of Pediatrics Committees: (1) test for susceptibility by performing a rubella hemagglutination-inhibition test, (2) if immune, do not vaccinate, and

(3) if susceptible, vaccinate only if pregnancy can be avoided during the subsequent 2 month period. During the past year many hundreds of women had therapeutic abortions because they became pregnant after receiving rubella vaccine without a previous test for susceptibility. It is likely that a hemagglutination-inhibition test would have revealed evidence of immunity in 85 to 90 per cent of them. The incredible toll in terms of unnecessary anxiety and cost could have been prevented by the performance of this simple, highly specific, relatively inexpensive test.

During the 1964 rubella epidemic physicians were helpless in their efforts to protect susceptible pregnant women. The use of many thousands of doses of gamma globulin had little effect on the incidence of congenital rubella. The development and recent licensure of live attenuated rubella vaccines represents an historic event in the field of preventive medicine. The appropriate use of these vaccines should have a major impact on the control of the rubella problem.

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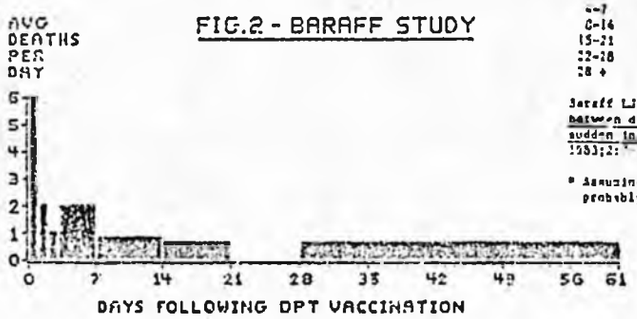
As it turns out, a number of surveys exactly like this have actually been performed, and the results are graphed in Figures #2-#6. Figures #2 through #5 obviously show a very large number of deaths occurring in the first few days following DPT. These are not "bumps" in the graphs; they are mountains.

FIG.2 - BARAFF STUDY



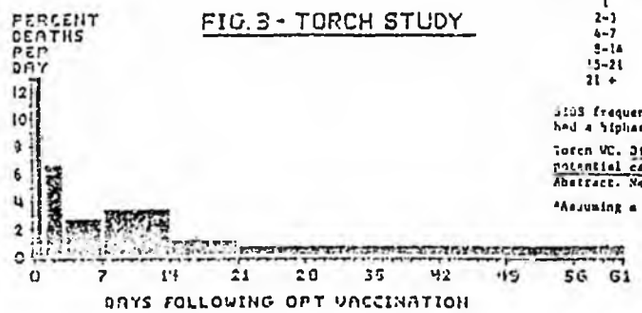
53 of 145 SIDS victims had received DPT:

Days from DPT to Death	Number Deaths	Avg.Num per Day
1	6	6
2	2	2
3	1	1
4-7	8	2
8-14	6	0.86
15-21	4	0.57
22-28	0	0
28 +	26	0.78*

Baraff LJ, Ablon WJ, Weiss RC. Possible temporal association between diphtheria-tetanus toxoid-pertussis vaccination and sudden infant death syndrome. Pediatric Infectious Disease 1983;2: 11.

* Assuming a maximum number of 61 days between DPT and SIDS; probably a conservative assumption.

FIG.3 - TORCH STUDY



2/3 of 70 SIDS cases had received DPT:

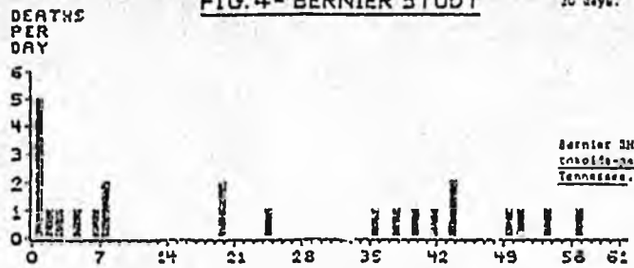
Days from DPT to Death	% of Cases	% per Day
1	13	13
2-3	13	6.5
4-7	11	2.75
8-14	24	3.43
15-21	9	1.29
21 +	30	0.75*

SIDS frequencies peaked at age 2 months in the non-DPT group and had a biphasic peak occurrence at 2 and 4 months in the DPT group.

Torch WC. Diphtheria-pertussis-tetanus (DPT) immunization: a potential cause of the Sudden Infant Death Syndrome (SIDS). Abstract. Neurology 1982;32:A149.

*Assuming a maximum number of 61 days between DPT and SIDS.

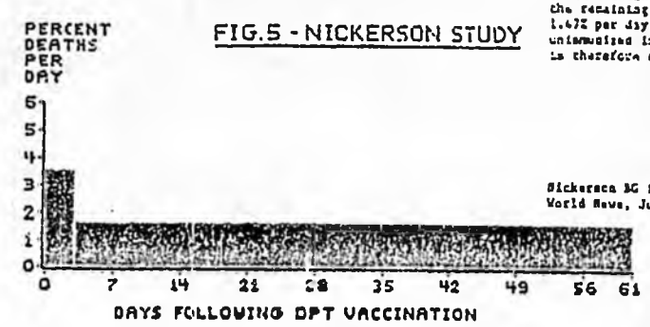
FIG.4- BERNIER STUDY



33 of 35 SIDS victims had received DPT; the number of deaths as shown were recorded on a per day basis. An additional 9 deaths occurred between 61 and 140 days, or on the average 1 every 10 days.

Bernier RH, Frank JA JR, Bondurant TJ Jr et al. Diphtheria-tetanus toxoids-pertussis vaccination and sudden infant deaths in Tennessee. Journal of Pediatrics 1982 101:419-421.

FIG.5 - NICKERSON STUDY



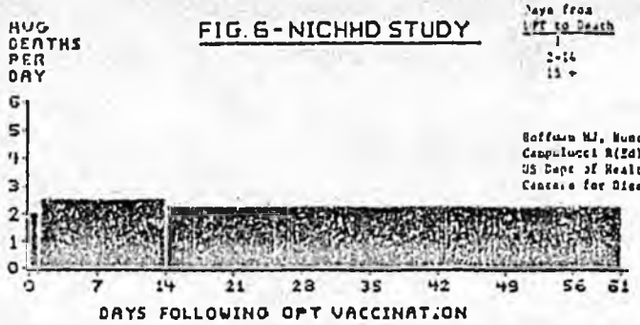
Of 601 SIDS victims 10.4% died within 72 hours of immunization, or an average of 3.47% per day. Assuming a baseline of 61 days the remaining 89.6% of deaths would occur at an average rate of 1.47% per day. NOTE: This group includes both immunized and unimmunized infants; the clustering effect in the first 3 days is therefore assumedly "diluted".

Dickerson BG Jr: SIDS-Immunization Link Questioned. Medical World News, June 10, 1985.

Could these "mountains" have occurred just by chance? The answer is yes, but the likelihood of their occurrence by chance is extremely small. Dr. Baraff, for example, calculated the chances of finding 6 of 53 deaths occurring on the day of the shot to be less than 1 in 2000. Dr. Daniel Shannon of the NEIDSF calculated a very similar probability with regard to the data of the Bernier study. That is a very small probability, and the probability of obtaining virtually the same results by chance alone in 4 independent surveys is smaller still---ridiculously small. The obvious explanation of course is that DPT is causing some deaths that are rightly or wrongly called SIDS. If DPT did not cause these "mountains", what did?

But what about Figure #6, the NICHHD study? Here is a large-scale study, conducted by a whole panel of SIDS experts, which demonstrates no apparent connection between DPT and SIDS. The number of deaths per day is almost perfectly uniform. How can this discrepancy be explained? Is this study right and the others wrong, or vice versa? Or was a different method used in the NICHHD study which might help to explain how such an opposite conclusion could be reached?

FIG. 6 - NICHHD STUDY



163 of 380 SIDS victims had received DPT. Cases screened from study included infants on whom no autopsy was performed and infants whose autopsies exhibited "major deviations from standardized autopsy protocol".

Days from DPT to Death	Number Deaths	Avg. Num per Day
1	2	2
2-14	33	2.54
15 +	130	2.34

Hoffman HJ, Hunter JC, Hasselmeyer EG. SIDS and DPT. In: Campbell-Reid R(Ed). 17th Immunization Conference Proceedings. US Dept of Health & Human Services, Public Health Service, Centers for Disease Control, Atlanta, Ga. 79-88.

The answer here is that the NICHHD study did in fact employ a different method than the other 4 surveys, and the difference lies in the method of selecting SIDS cases for study. Whereas Baraff, Torch, Bernier, and Nickerson counted any and all infants in the time period and area under examination who were reputed to have died of SIDS, i.e. whose death certificates read "SIDS" or "crib death", the NICHHD panel screened out certain cases beforehand. Some excluded from study were infants on whom no autopsy had been performed, and infants whose autopsies contained findings that varied from a "standardized" SIDS autopsy as defined by the panel. It is extremely common for autopsies of "suspicious DPT-SIDS" victims to contain deviations from the classic SIDS autopsy; a few examples of such non-SIDS findings (of the many we are personally aware of) are encephalopathy of the brain and cerebral hemorrhage. The question is: which types of cases did the NICHHD panel exclude and which did they include in their prescreening process? Unfortunately, despite repeated attempts to have this question answered, no reply has been forthcoming. Did the NICHHD, perhaps unwittingly, "load the dice" by excluding from study those cases they needed most to include? And where does this leave the parents of babies whose deaths have been ruled SIDS by the local coroner, and are now ruled not SIDS by the NICHHD? It is important to underscore: If the NICHHD did inadvertantly exclude DPT deaths (ruled SIDS) by excluding atypical autopsies, when Baraff, Torch, Nickerson, etc. included these atypical autopsies, this would explain the apparent contradictions in findings, and lead us to suspect that: indeed DPT does not appear to cause real SIDS deaths, but some DPT deaths are being misdiagnosed as SIDS. And a footnote on the apnea babies (used to be called "near-SIDS-miss") with regard to all of this: current research is only finding a 5% overlap between apnea-suffering babies and SIDS victims. This overlap is so small that we would not expect any of the studies we've discussed to clearly demonstrate DPT risk for apnea-prone babies. Until more studies on the effect of DPT on such babies are done, we are left with Dr. Shannon's frightening experience where about 20% of such babies required resuscitation within 24 hour of DPT.

The jury is still out on the question of whether or not DPT causes some real SIDS deaths. There are many, including Dr. Loring Dales, head of immunization for the state of California, for whom the NICHHD does not settle this issue: "...enough other evidence exists to cause continued concern that the vaccine may rarely cause SIDS, so that need is felt for continued investigation of the matter...". (Source: Dales, L. 1984. Pertussis Vaccine and SIDS. Cal. State Dept. Health Services: SIDS Newsletter, Summer, 1984.)

A final note on the studies: the experts have engaged in a lot of debate over the merits of the various studies. Baraff and Torch, for example, have been criticized for not using a "case-control" method, like that used by the NICHHD. And yet Alvan Feinstein, Professor of Medicine at Yale, and a widely respected authority on medical statistics, said about the "case-control" method: "hidden bias can substantially distort the results." This is a particular danger when a group is treated as being homogenous when it is really comprised of many different entities. Everyone agrees that SIDS is a catch-all term for many different causes of death, i.e. SIDS victims are not a homogenous group.

The debate over study design can go on (and will) indefinitely, and is beyond the scope of this brochure. Meanwhile, babies are dying. It is true that Baraff and Torch had no control groups, but it is equally true that no plausible explanation for their findings, outside of DPT's responsibility, has ever been advanced. "It's all a coincidence" is hardly a plausible explanation. The treasure of our babies' lives deserve a better explanation than that, and immediate intensive research.

A final note: The poor quality of SIDS autopsies and the misclassification of DPT deaths as SIDS is hindering progress on the prevention of many types of infant deaths. If we could exclude DPT (and other non-SIDS) deaths from SIDS studies, true SIDS risk factors would be more likely to become clear. The DPT (and other non-SIDS) victims could be "cloudying the water," and postponing the discoveries that will save babies' lives.

1986 UPDATE

The "abstract" of the Nickerson study has been published (Nickerson BG, Robinson BK: How many Sudden Infant Death Syndrome victims were recently immunized? Abstract, A261, J Soc Ped Res).

Nickerson concludes that "a relationship between SIDS and immunization accounts for less than 6.3% of total SIDS deaths." If we apply his finding of an approximate 6% excess of deaths beyond those expected by chance within 3 days of DPT, to the 8,000-10,000 estimated deaths ruled SIDS (correctly or not) each year, we find 480-600 babies in the U.S. each year whose deaths are "vaccine-related".

This study raises serious questions about the DPT benefit/risk ratio, as CDC has estimated 450 deaths from whooping cough per year in the absence of pertussis vaccine. (Hinman A et al. 1984. Journal of the AMA 251(23): 3109-13.)

Case	Pregnancy	Birth	Health from birth to 1st DPT	Age & health at time of 1st DPT	Reactions	Interval DPT to death	Coroner ruling	Family History: Allergy	Family History: Severe DPT Reaction	Family History: Epilepsy	Family History: Other
Baby Girl 1	uneventful	normal	excellent	2 months; healthy	leg twitching; strange screaming; did not eat	10 hours	SIDS	asthma, excema, allergies	yes	yes	
Baby Girl 2	uneventful	normal	problems with formulas; otherwise excellent	2 months; had a cold; otherwise healthy	extreme paleness; unresponsive; oversomnolence; unconcolable screaming	6½ days	SIDS	allergies incl. cow milk			migraine
Baby Boy 3	uneventful	normal	excellent	2 months; had a cold; otherwise healthy	unconsolable screaming	12 hrs	SIDS	cow milk allergy			
Baby Boy 4	uneventful	normal	excellent	2 months; healthy	high pitched screaming; limpness; diarrhea; cold extremities	33 hrs	irreversible shock due to probable DPT reaction	milk intolerance	yes	yes	migraine
Baby Boy 5	uneventful	normal C Sec (labor failed to progress)	excellent	2 months; healthy	repeated bouts of high pitched screaming	15 hrs	SIDS				diabetes
Baby Boy 6	uneventful	routine repeat C Sec; TTN; O_2 support 6 hrs; Apgar 9,9	resolving breast jaundice; otherwise excellent	1½ mo; trace of jaundice; end of ear infection; otherwise excellent	unconsolable crying; jerking of extremities with high pitched vocalizing, staring, diarrhea, limpness	5 days	SIDS	cow milk & other allergies	yes, & severe reaction to other vaccines		migraine convulsions
Baby Boy 7	uneventful	vaginal; breathing support req. briefly; discharged 48 hrs after birth	Hosp 3 days w/ virus at age 2 mos; otherwise healthy	3 months; healthy	excessive sleeping; eyes bloodshot & swollen; congestion; episodes of eye-crossing; terrible cough	10 days	SIDS	asthma; excema; food allergies	yes		convulsions
Baby Girl 8	uneventful	normal	excellent	3 months; end of cold/ runny nose; otherwise healthy	terrible screaming; limpness	4 hours	SIDS	asthma; excema; allergy incl. cow milk	yes	yes	
Baby Girl 9	uneventful	normal	excellent	2 months; at end of cold; otherwise healthy	back arched scream at time of shot; eyes rolled up; high pitched unconsolable scream	3 hours	SIDS				migraine

Neurology 1982

SESSION ON CHILD NEUROLOGY I

Morning Meeting

Friday, April 30 9:30 AM—11:45 AM (Alexandria)

Chairman: Robert Vannucci, Hershey, PA
Secretary: Jay Pettegrew, Dallas, TX

8:00 AM	Poster Presentations III	(Washington Ballroom)
8:30 AM	Exhibits	(Hall B)
9:00 AM	S. Weir Mitchell Award Essay	(Sheraton Ballroom)

Duration of Therapy for Neonates with Seizures

9:30 AM 1

LAURA R. MENT and SAMUEL L. BRIDGERS, New Haven, CT

Neonatal seizures constitute a significant problem in the Neonatal Intensive Care Unit (NICU) population, occurring in approximately 3% of neonates admitted to our NICU. Varying recommendations have been made on the duration of anticonvulsant therapy following neonatal seizures. Concerns over adverse effects of phenobarbital on developing infants must be balanced against the likelihood that seizures will recur without medication. Infants treated in our NICU for neonatal seizures were tapered off phenobarbital if they had normal neurologic examination and normal EEG at corrected age 3 months, and no history of seizures since discharge. In the 23 infants fulfilling these criteria, with mean birthweight of 2810 grams (range, 630 to 4120 gm) and mean gestational age at birth of 37 weeks (range, 25 to 43 weeks), seizure etiologies included asphyxia (9), intracranial hemorrhage (4), familial neonatal seizures (2), metabolic abnormalities (2), sepsis (1), infarct (1), narcotic withdrawal (1), and undetermined (3). With a mean follow-up to age 13 months (range, 6 to 29 months) in 22 infants, none has suffered recurrent seizures. A normal 3-month evaluation allows safe withdrawal of anticonvulsants in infants with a history of neonatal seizures, regardless of etiology.

Generalized Neonatal Seizures in Primates: Focal Inhibition of Protein Synthesis in Vulnerable Regions

9:45 AM 2

C.G. WASTERLAIN and B. DWYER, Los Angeles, CA

A new method for quantitative autoradiographic measurement of brain protein synthesis with I-[^{14}C]-valine was used to study twin pairs of newborn marmoset monkeys (4 to 7 days old) and rats (4 days old) during generalized bicuculline seizures (5 mg per kilogram IP 30 minutes). In controls, the rate of [^{14}C]-valine incorporation into proteins was high in hippocampal cell bodies and in some layers of the lateral geniculate nuclei; slightly lower in cortex, moderately lower in caudate and thalamus, and considerably lower in white matter. In marmosets, seizures resulted in a profound inhibition of protein synthesis in hippocampus and cortex, while some layers of the lateral geniculate nuclei remained extremely active in protein synthesis and other regions showed intermediate changes. These regional variations were much less striking in rats.

The remarkable focality of the inhibition of brain protein synthesis in generalized bicuculline seizures in primates may bear a relationship to the selective vulnerability of some neuronal populations to epileptic damage.

Diphtheria-Pertussis-Tetanus (DPT) Immunization: A Potential Cause of the Sudden Infant Death Syndrome (SIDS)

10:00 AM 3

WILLIAM C. TORCH, Reno, NV

A recent report of eight DPT-associated cot deaths in Tennessee, and knowledge of four sudden deaths within 3½ to 19 hours of inoculation in Nevada (in three infants and one 3-year-old child) stimulated a study on the relationship of SIDS to DPT immunization in over 200 randomly reported SIDS cases. Preliminary data on the first 70 cases studied shows that ⅔ had been immunized prior to death. DPT #1, 2, and 3 were administered on the average at age 2, 4, and 6 months, respectively. In the DPT SIDS group, 6.5% died within 12 hours of inoculation; 13% within 24 hours, 26% within 3 days, and 37%, 61%, and 70% within 1, 2, and 3 weeks, respectively. Significant SIDS clustering occurred within the first 2 to 3 weeks of DPT #1, 2, 3, or 4. The age range of the DPT group was 59 days to 3 years (mean age, 3 months); for the non-DPT group, 17 to 172 days (mean age, 2 months). SIDS frequencies peaked at age 2 months in the non-DPT group, and had a biphasic peak occurrence at 2 and 4 months in the DPT group. DPT #1 and 2 were associated with more SIDS than #3 or 4 (ratio 30:11:4:1). Males and females were equally affected. Cot death occurred maximally in the fall winter season in the non-DPT group, but was nonseasonal in the DPT group. Death occurred most often in sleep in healthy allergy-free infants following brief periods of irritability, crying, lethargy, upper respiratory tract symptoms, and sleep disturbance. Autopsy findings in both groups were typical of SIDS, (e.g. petechiae of lung, pleura, pericardium, and thymus; vascular congestion;

pulmonary edema; pneumonitis; and brain edema). In conclusion, these data show that DPT vaccination may be a generally unrecognized major cause of sudden infant and early childhood death, and that the risks of immunization may outweigh its potential benefits. A need for reevaluation and possible modification of current vaccination procedures is indicated by this study.

Local Cerebral Glucose Utilization in the Beagle Pup Model of Intraventricular Hemorrhage

10:15 AM 4

LAURA R. MENT, CHARLES C. DUNCAN, RICHARD LAMBRECHT, and WILLIAM B. STEWART, New Haven, CT, and Upton, NY

Intraventricular hemorrhage (IVH) is a major neurologic problem of preterm infants and is thought to be a manifestation of alteration in blood flow to the germinal matrix. Neonates with IVH often have long-lasting hypoglycorrhachia, which may imply profound alterations in cerebral metabolism. Such metabolic alterations could have significant neurodevelopmental consequences. Therefore, we have utilized the ^{14}C-2-deoxyglucose (2DG) method to study local cerebral glucose utilization (LCGU) in the beagle pup model of IVH. Six pups (12 to 48 hours, 300 to 425 gm weight) were anesthetized, tracheotomized, paralyzed, and ventilated. Arterial blood gases and blood pressure were obtained through a femoral artery cannula. IVH was induced (and later documented by neuropathology) by removal of 20 to 25% of their total blood volume via a femoral venous catheter, followed by rapid venous reinfusion 5 minutes later. Five additional pups served as controls. In the hemorrhage pups, MABP was 80 mm Hg prior to the withdrawal of the blood, 65 mm Hg during the hypotensive phase, and 93 mm Hg following reperfusion. Control pups had MABP 82 mm Hg throughout. Fifty minutes following the induction of IVH, LCGU was measured. ^{14}C-2DG concentrations were 23, 12, 20, and 18 μCi for the cortex, white matter, caudate nucleus, and germinal matrix, respectively, of the controls. For the experimental group, 2DG concentrations included cortex, 19; white matter, 17; caudate nucleus, 19; and germinal matrix, 17 μCi. In the presence of IVH, LCGU throughout the brain becomes homogeneous, and although cerebral blood flow changes may be localized to specific regions of hemorrhage in this model of IVH, there may be an uncoupling of blood flow and metabolism throughout the brain.

The Cerebrophysiologic Response of Neonatal Dogs to Graded Hypertension

10:30 AM 5

RICHARD S. K. YOUNG, SUSAN K. YAGEL, and RUDOLFO AZZIZ-BAUMGARTER, Hershey, PA

We have previously determined regional cerebral blood flow (CBF) in the newborn dog during normotension and hypotension. We have now measured the cerebral physiologic responses of newborn dogs to graded hypertension, using an autoradiographic method with ^{14}C-iodoantipyrine as indicator. Newborn mongrel dogs (1 to 10 days of age) were given an intravenous infusion of metaraminol (0.041 to 0.082 mg per kilogram per minute) to raise mean arterial blood pressure (MABP) from 61 ± 5 to 91 ± 3 or 105 ± 6 mm Hg ($p < 0.001$). These elevations in MABP led to widespread increases in CBF, particularly in diencephalon (thalamus: from 22 ± 10 to 56 ± 13 ml/100 gm/min, $p < 0.001$), brainstem (medulla: from 28 ± 10 to 74 ± 22 ml/100 gm/min, $p < 0.001$), and cerebral white matter (from 6 ± 2 to 12 ± 3 ml/100 gm/min, $p < 0.001$). In addition, all animals developed marked subarachnoid or intraventricular hemorrhage.

In the newborn dog, CBF is held constant or "autoregulated" at MABP of 30 to 80 mm Hg. Although hypotension leads to reductions of CBF only in periventricular and occipital white matter, hypertension produces widespread increases in CBF. These findings suggest that periventricular leukomalacia is related to cerebral ischemia, while cerebral hemorrhage results from acute increases in CBF.

The Effect of Glucose Supplementation on Neonatal Hypoxic-Ischemic Brain Damage

10:45 AM 6

THERESA VOORHIES, DONALD G. RAWLINSON, and ROBERT C. VANNUCCI, New York, NY

The observation that glucose treatment increases the survival of hypoxic perinatal animals provides the rationale for the administration of glucose to asphyxiated newborn infants. However, studies in adult animals suggest that glucose supplementation accentuates hypoxic-ischemic brain damage. To resolve the apparent paradox, 7-day postnatal rats underwent right common [illegible]. Histologic analysis revealed alterations only in those rats subjected to both carotid artery ligation and hypoxia. Infarction ipsilateral to the arterial occlusion occurred in 50% of both glucose-treated animals (four of eight) and saline controls (three of six). In all the glucose-treated animals, infarction involved the entire territory of the right middle cerebral artery, whereas in only one

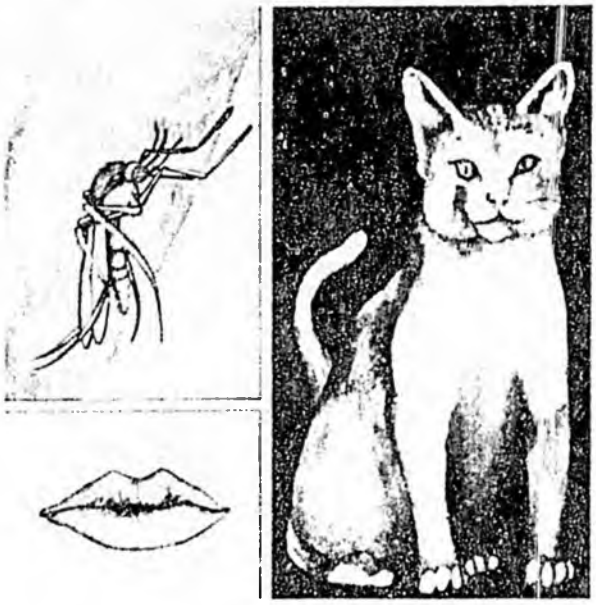
Surgeon General's Report on

ACQUIRED IMMUNE DEFICIENCY SYNDROME

cuts to the blood or other body fluids of the infected child a highly unlikely occurrence. Even then routine safety procedures for handling blood or other body fluids (which should be standard for all children in the school or day care setting) would be effective in preventing transmission from children with AIDS to other children in school.

Children with AIDS are highly susceptible to infections, such as chicken pox, from other children. Each child with AIDS should be examined by a doctor before attending school or before returning to school, day care or foster care settings after an illness. No blanket rules can be made for all school boards to cover all possible cases of children with AIDS and each case should be considered separately and individualized to the child and the setting, as would be done with any child with a special problem, such as cerebral palsy or asthma. A good team to make such decisions with the school board would be the child's parents, physician and a public health official.

Casual social contact between children and persons infected with the AIDS virus is not dangerous.



Insects

There are no known cases of AIDS transmission by insects, such as mosquitoes.

Pets

Dogs, cats and domestic animals are not a source of infection from AIDS virus.

Tears and Saliva

Although the AIDS virus has been found in tears and saliva, no instance of transmission from these body fluids has been reported.

AIDS comes from sexual contacts with infected persons and from the sharing of syringes and needles. There is no danger of infection with AIDS virus by casual social contact.

Testing of Military Personnel

You may wonder why the Department of Defense is currently testing its uniformed services personnel for presence of the AIDS virus antibody. The military feel this procedure is necessary because the uniformed services act as their own blood bank in a time of national emergency. They also need to protect new recruits (who unknowingly may be AIDS virus carriers) from receiving live virus vaccines. These vaccines could activate disease and be potentially life-threatening to the recruits.

opinion will be a much more phenomenon in American life than the person who the opinion himself, Bruce

is no question that Franklin pular and effective teacher. He as one student put it, the only at Stanford who both advo- d lived according to Marxist d thus exposed students to principles in a fashion that no ully committed was capable of. was perhaps inevitable that who had the habit of signing his letters "death to all Fascist pigs" and frequently identified the university as part of an educational-industrial complex that he held responsible for the Vietnam war, should clash with the Stanford administration, who correctly identified Franklin's long-range goal as stopping the "normal" activities of the university.

Dershowitz and other civil libertarians have pointed out that the quasi-legal nature of campus hearings—which exclude, for example, the right to challenge prospective jurors—provides fewer guarantees of due process than exist in criminal law. Thus the dismissal of persons such as Franklin for "just cause," as interpreted by most faculty members in U.S. colleges and universities, may nonetheless result in the weakening of academic freedom. Disagreeing with this view, however, advisory board chairman Kennedy told *Science* that, his dissent on Franklin's dismissal notwithstanding, he believes existing procedures do protect academic freedom. The result at Stanford, in any event, has been to leave the university a quieter, but possibly less interesting, place.—ALLEN L. HAMMOND

Division of Biologics Standards: The Boat That Never Rocked

can be few graver opportu- r man-made disaster than the munization campaigns that are line in many countries. Should cine preparations become con- d with an undetected agent in the host cells, such as a using virus, a whole genera- vaccinees could be put in jeop- his, of course, is no science writer's horror story—it has al- appened once; millions of peo- e been injected with a monkey own as SV40, which was found to be contaminating polio and rus vaccines. The virus causes in hamsters; no one yet knows may do in man.

of forswearing all vaccines and the return of epidemic dis- he necessary safeguard against ccidents is vigilant surveillance earch. The government institu- trusted with this duty is the n of Biologics Standards (DBS), an agency set on the campus National Institutes of Health, in a, Maryland. The DBS has re- been the focus of unfavorable . A Civil Service grievance ee recommended censure of the 's management for allowing a research scientist, J. Anthony to be harassed by his super- (*Science*, 25 February), and and his attorney, James S. have accused the DBS of scientific mismanagement in a document made public by Senator Abraham Ribicoff (D–Conn.) (*Science*, 3 March). The significance of the specific charges raised by Morris and Turner has yet to be determined, but their indictment prompts a number of general questions about the role of the DBS in vaccine regulation. How well has the DBS research program been managed? What are the important decisions that have faced the DBS and how has it approached them? What kind of a track record does the division have in fulfilling its regulatory responsibilities?

These questions are hard to answer from the outside, in part because of the clublike, partly closed nature of the vaccine community. Federal responsibility for vaccines does not rest solely on the DBS, but is diffused over a handful of committees with interlocking memberships. Thus, if the mass annual inoculations against influenza were indeed the "forcing on the public [of] a bogus situation. . . . The vaccine we were promoting was not having any beneficial effects,"* it is not too clear whether responsibility would lie with the DBS for certifying an inefficacious vaccine or with a second body, the Center for Disease Control's Advisory Committee on Immunization Practices (ACIP), whose function is to decide who should be vaccinated against what. Again, when the typhus vaccine shot into every U.S. Army recruit since World War II turned out in 1969 to be producing insufficient antibody even though it had regularly passed the DBS tests, it was unclear whether the DBS or the Armed Forces Epidemiological Board (AFEB) should claim fatherhood of the fiasco. Federal responsibility for the development of new vaccines is notably imprecise. Both the DBS and another segment of the NIH, the Infectious Diseases Branch of the National Institute of Allergy and Infectious Diseases, are permitted to develop new vaccines, but neither has specific responsibility for doing so.

Besides the haziness of responsibility, the picture is also blurred by a reluctance among vaccine workers to discuss problems openly when they arise. This is because of the understandable fear that public confidence in vaccines—and vaccine authorities—will be eroded. As one participant—in fact, the chairman of the NIH committee that studied the Morris-Turner charges—said at a recent conference on vaccines: "From our debates on what is best or what is wrong, we are conditioning the public to reject measures that sometimes, in some situations, are very important."† The importance attached to presenting an unruffled surface to the public is exemplified by the SV40 incident of 1961; even when the contaminating virus was found to be oncogenic in hamsters, the DBS and its expert ad-

* A. D. Langmuir, *International Conference on the Application of Vaccines* (Pan American Health Organization, Washington, D.C., December 1970), p. 614. Langmuir, now at the Harvard University Medical School, was formerly head of the epidemiology branch of the Center for Disease Control at Atlanta, Georgia.

† A. S. Benenson, *International Conference on the Application of Vaccines* (Pan American Health Organization, Washington, D.C., December 1970), p. 612.

visory committee decided to leave existing stocks on the market rather than risk eroding public confidence by a recall. Even after the polio accidents of 1955, the scandal that led to the creation of the DBS from the former Laboratory of Biologics Control, continuity was stressed as much as change; the assistant chief of the laboratory, Roderick Murray, became the director of the DBS, and the chief of the laboratory became a lab chief in the DBS.

None of this implies that faults have been covered up or that the public has been conspired against in any way; but there are dangers that problems will be underemphasized in any system that discourages the fullest possible discussion, as some believe the DBS does. For instance, a recent article on the reactions associated with viral vaccines concludes: "There has been a tendency on the part of certain higher government circles to play down any open discussion of problem- ated with vaccines. . . . Perhap. is has been overdone. Scientists now find themselves in the position of balancing the benefits of a vaccine against the risks, yet are in no position to judge what the long-term risks are."‡

Evaluating the risks of vaccines is one of the tasks of the DBS, which is charged with ensuring the safety and quality of biological products. Of the six laboratories of the DBS, one deals exclusively wtih blood products, one with inspection and control activities, and the remaining four with vaccines. For fiscal 1972 the DBS has a budget of just over $9 million, of which roughly $2 million is devoted to an extramural contract research program. The in-house budget of the DBS is split roughly equally between research and control activities (no exact figure is available).

Without doubt the DBS has capably fulfilled its minimum function, that of ensuring the immediate safety of vaccines. What is at question is whether the DBS has adequately carried out such broader responsibilities as improving the quality of vaccines and assessing the longer term risks and benefits associated with vaccine use. To carry out such responsibilities, the DBS might be expected to support an aggressive, centrally directed research program, closely coordinated with regulatory decisions.

In fact, the DBS research program is neither evidently aggressive, nor strongly directed, nor ranked in equal importance with regulatory activities. The attitude of the present management toward research is more one of toleration than active encouragement. Over the last decade, DBS Director Roderick Murray has not been notably successful in increasing the DBS's research competence. Although Murray has been director since 1955, when the DBS was created, the division in its early years was closely supervised from the NIH front office by James A. Shannon, then director of the NIH, and associate director Joseph E. Smadel. Smadel eventually transferred to the DBS as a laboratory chief, from which position he, in effect, directed the division until his death in 1963. During this period, the DBS staff grew from 54 to 249 positions; between 1963 and the present, the DBS has enjoyed a net increase of 11 persons, although its responsibilities have grown in far greater proportion. The only major growth in DBS research activities since 1963 was the establishment of the contract research program in 1966. But the program originated from elsewhere on the NIH campus and was assigned to the DBS by the NIH front office.

Headless Research Program

What many consider to be a major structural weakness in the present DBS research program is the absence of a scientific director. Although this function might be expected to be performed by the director of the DBS, Murray has left the planning of research to the initiative—some say the whims—of the laboratory chiefs. The only attempt at central coordination of research was in 1966, when the NIH front offi e assigned Leon Jacobs, a toxoplasma expert, to direct the new contracts program. Jacobs also took the title of scientific director, but left the DBS within 2 years, apparently because Murray allowed him no authority over the inhouse research program. The NIH front office (where Jacobs is now assistant director for collaborative research) has made no attempt to install a second scientific director of the DBS, presumably because of the experience of the first.

Despite the absence of central direction, some DBS scientists believe the various lab chiefs have coordinated their activities to cover all the essential areas of research, at least in relation [illegible] staff. Others con-

lowed to develop. Says f[illegible] scientist Kendall O. Smith[illegible] fessor of microbiology at th[illegible] of Texas Medical School, S[illegible] "There are inexcusable gaps [illegible] research program, specifical[illegible] to the safety of the viral sul[illegible] to grow vaccines. It's on[illegible] ultraconservatism that mak[illegible] less obvious than they ar[illegible] former DBS scientist, B.[illegible] now chairman of the micr[illegible] partment at the University [illegible] criticizes the scanty efforts [illegible] ticipate research problems. [illegible] time the DBS got upset w[illegible] before something came u[illegible] ing," Young told *Science*.

Specific research areas [illegible] the DBS coverage is mos[illegible] faulted are the improvemen[illegible] vaccines, particularly influe[illegible] tussis, the hypersensitivity [illegible] associated with certain kil[illegible] and the study of the vario[illegible] and other viruses that are [illegible] taminants of vaccines.

Besides lacking scienti[illegible] the DBS research progra[illegible] ably also suffered, or fail[illegible] from the use made of the [illegible] of scientific counselors. A[illegible] inally constituted to look [illegible] search program of the [illegible] board has, according to M[illegible] only one real suggestion [illegible] and even that was not [illegible] Since membership is dra[illegible] ranks of the most distin[illegible] tists in the vaccine fiel[illegible] would not seem to have [illegible] the best possible advan[illegible] present members compla[illegible] have been used only as [illegible] board," and clearly the [illegible] DBS research program [illegible] very different if the boa[illegible] existed.

Research Findings Un[illegible]

Potentially more seriou[illegible] organizational weakness [illegible] sources is the attitude [illegible] agement toward research [illegible] have implications for re[illegible] sions. There is no proof [illegible] management has delibera[illegible] suppressed scientific da[illegible] seems to have been a cu[illegible] seeking out or pursuing [illegible] with implications for a[illegible] cision. Present and form[illegible] tists repeatedly use the [illegible]

toward research that might lead
regulatory change or decision.
ding to C. W. Hiatt, formerly
chemist at the DBS and now at
niversity of Texas Medical School,
ntonio, "The intellectual attitude
DBS management was not hos-
long as your research didn't rock
at. We only got ourselves tangled
en we got involved in any way
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were very, very few. But there
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a scientist who is still with the
The DBS is negative toward re-
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is something about Murray that
comes back to the same theme,
rock the boat.'"
Young, a former DBS scientist
is endorsed the Morris-Turner
ns of the DBS management, de-
the DBS attitude toward re-
as being one of "suppression,
ent, and censorship of individ-
stigators such as Morris, Eddy,
nd Hiatt. I finally came to rea-
you had either to compromise
or leave. Morris and Eddy are
heroes in that place because
yed and fought. The others
ith their feet and left."
s has stated that he was re-
rom influenza control duties
he raised questions about the
of the vaccine. Eddy was de-
fter demonstrating in 1961 that
us causes tumors in hamsters.
liatt, and Young left the DBS
ng reasons, but each had dif-
ongly with the DBS manage-
er particular research issues
felt should prompt a regula-
sion. Hiatt, as senior chemist
S, believed that manufacturers
e required to institute a stan-
strial check test to ensure that
servatives had not been added
es. "Most chemists with any
industrial background would
in not insisting that this kind
ing be followed," Hiatt told
"but the management felt I
erating its importance."
ecific issue that concerned
the procedure for screening
y cells used in growing vac-
detect all the possible con-
taminating viruses, you need to hold the cells for much longer than the 2 weeks specified in the DBS regulations. One of the chief ways I became obnoxious to the DBS management was in continuing to press for a longer incubation time. I think it is unforgivable that the DBS did not change their regulations" Smith told *Science*.

What alarmed Young was the discovery by a DBS research contractor of herpes virus in the dog kidney cells in which it was proposed to produce rubella vaccine. Yet, Young says, he could not get the DBS authorities to investigate the matter further; "The DBS puts almost total trust in the manufacturers to do all the most important testing work. The DBS simply reads the manufacturers' protocols."

Part of the dissatisfaction felt by these scientists could be due to the apparent uncommunicativeness of the DBS management in explaining its actions. Murray, who in fact has delegated little if any of the decision-makng power in the DBS, is not by nature expansive. "Even those who work with him rarely know his opinion on a matter," says a colleague. Another factor in the distrust felt for the management's attitude toward research may be one related to the nature of scientists. "Scientists are particularly hard to direct unless they feel a certain amount of respect for the personality directing them," says one vaccine specialist. "Murray has done reliable, consistent work on hepatitis, but is not much known scientifically."

But the personnel problems of the DBS seem to go deeper than just the handling of scientists. The Morris grievance hearing last year resulted in a committee recommendation that the DBS management be censured for allowing Morris to be harassed. The NIH front office does not accept this verdict. Says Robert W. Berliner, NIH deputy director for science, "If the DBS deserves censure, it is because they tolerated Morris for as long as they did. Morris was disruptive, insubordinate, and failed to take adequate action to straighten out the problems of the flu vaccine potency." (Morris's position is that he did try to improve flu potency tests, even though DBS managers ignored the results of existing tests.) Morris, however, is not alone in finding the DBS management hard to live with; besides the scientists who have left, some 20 or so members of the present staff of the DBS are involved in personnel disputes of various degrees of severity.

How has the management of research contributed to the DBS decision-making process? Significantly, maybe, many of the most important decisions made by the DBS have been reached with the aid of large, often international, conferences. Murray says the licensing of live polio vaccine in 1961 was the hardest choice he has faced because there were three different virus strains from which to select, but he emphasizes that the decision was made on a collective basis, not by him alone.

Decisions on Rubella and WI-38

Another important decision was the licensing of rubella vaccine in 1969, when again there was a choice of virus strains—one developed by three scientists in the DBS (Harry M. Meyer, Paul D. Parkman, and Hope E. Hopps) and another by Stanley Plotkin of the Wistar Institute. There is no reason to suppose that individual DBS scientists acted other than entirely honorably, but the DBS as an institution was put in a classic conflict of interest position in having to decide upon a vaccine it had itself developed. The position was made the more invidious when a particular manufacturer, Merck Sharp and Dohme, abandoned its own strain of rubella virus in favor of that developed by the DBS. Even if Murray was scientifically justified in awarding the vaccine license to Merck Sharp and Dohme with the DBS virus strain, he failed to do so in a manner that was obviously fair to observers inside or outside the DBS. Says former DBS scientist Smith of the rubella decision: "The situation was not handled in a manner that could clearly be seen to be just. Murray must have seen it coming step by step. He could have stopped it but didn't." According to Paul S. Moorhead of the University of Pennsylvania and a member of the board of scientific counselors, "The handling of the rubella vaccine was an obvious conflict of interest and the DBS made no obvious attempt to head it off."

Perhaps the single most important decision to have faced the DBS—although Murray says he does not regard it as important—is that of whether to make vaccines in primary cells or in continuously passaged cells. In brief, the advantage of continuously passaged cells is that they can be exhaustively tested for normality, the absence of contaminating viruses, and so forth. By contrast, primary cells, which are taken directly from animal tissues such as

monkey kidney or duck eggs, may carry the viral flora unique to their host, yet for economic reasons can only be screened in a comparatively cursory manner. §

In 1962, a continuously passaged cell line derived from a human fetus was established by Leonard Hayflick, then at the Wistar Institute. Hayflick's cells, known as WI-38 cells, have been used for vaccines in other countries and, since 1965, by the U.S. Armed Forces. Yet the first WI-38 vaccine for U.S. civilian use was licensed by the DBS only last month.

Why did the DBS take a decade to make up its mind on WI-38 cells? Hayflick, now at the Stanford University School of Medicine, gave *Science* the following account of his efforts to persuade Murray to come to a decision on the cells. By 1963–1964, it had become clear, Hayflick says, that the DBS was highly resistant to licensing vaccines produced in WI-38 cells, though the reasons for this opposition were never stated. It was also clear that in most major vaccine developments embraced by the DBS, the primary risk-taking happened to have been borne outside the United States. (For example, live polio vaccine was licensed by the DBS after the Soviet Union had injected more than 15 million people. Live measles vaccine was first tested out, not on U.S. citizens, but on the inhabitants of the Upper Volta.)

Since it seemed that U.S. citizens would not get the benefit of WI-38 cells until foreign countries had taken the risk, Hayflick told *Science*, he organized an international committee called the Cell Culture Committee, to promote the use of WI-38 cells abroad. In 1967, Yugoslavia became the first country to license WI-38–grown polio vaccine. The U.S.S.R. adopted the cells in 1970, and England and France followed suit in 1971.

There is a respectable reason for being wary of WI-38 cells—the theoretical possibility that they might contain a human cancer agent somehow more insidious than those known to exist in animal cells. The DBS could be respected if it had taken this position, but, surprisingly, Murray has never taken any position at all on WI-38 cells, on the grounds that no manufacturer has applied to produce a WI-38 vaccine. To Hayflick, this is simply a stratagem for refusing to discuss the issue because, he says, no manufacturer would risk investing in a new type of vaccine before getting "an informal reading in face-to-face confrontation that Murray will be amenable." A nonscientific reason in persuading Murray to reverse his position may have been pressure from manufacturers who, according to *Drug Research Reports* (21 July 1971), said they would quit making polio vaccine unless allowed to do so in WI-38 cells.

Asked what new scientific facts had come to light to justify reversal of the DBS position, Murray told *Science* only that the "DBS acted promptly to move towards the problems of licensing such a product when it received a license application." Says a senior scientist in the DBS: "To this day I don't know what Murray thinks about WI-38 cells and I don't know why he has decided to license them now. It's another breakdown in communication. By refusing to discuss controversial issues, Murray has many times made the controversy worse."

Since many of the accidents with vaccines have occurred when new processes were introduced, it is probably sound policy not to make changes unless there are clear benefits in sight. Murray is widely praised, for example, for his refusal to allow mineral oil adjuvants to be put into vaccines, despite heavy pressure from manufacturers and parts of the academic community. (Oil adjuvants were recently tried in England with adverse results, an experience that has validated Murray's position.) No one disputes the fact that Murray practiced a conservative policy as director of the DBS, but some see his conservatism in a positive, others in a negative light. Vernon Knight, chairman of the microbiology department at the Baylor University College of Medicine, Houston, says of Murray: "He has a record of absolute honesty and total devotion to protecting the public. If there is any criticism, it is that he has been overdeliberate. But frankly, that is the way to stay alive in this business." Another view is that of Paul S. Moorhead: "If Murray does nothing, he doesn't get much criticism; but if he makes an innovation, then he is really under pressure." According to former DBS scientist Kendall O. Smith, "About 90 percent of the problems in this field will work themselves out if left alone. If you don't change much, you don't risk much. I feel that people have admired as Murray's servatism is only his inability to leadership in a growing field." one scientist acquainted with the "Murray doesn't really make decis So people don't realize from the ou that things don't really happen u there is a broad consensus both i and outside the DBS."

Problems with Potency

Failure to make certain impo scientific decisions openly and fr position of evident strength is pro one consequence of a weakly ma in-house research program. Anot the sometimes weak-kneed stanc DBS has taken in persuading man turers to improve the quality of vaccines. In ensuring vaccine safet DBS has a record blemished onl errors that sprang from the sta knowledge at the time. (These ar SV40 incident of 1961, the hyper tivity caused by the killed measles cine used in the early 1960's, an the opinion of some, the licensi a rubella vaccine which was grov dog kidney cells and which cause expectedly severe side effects.) Bu DBS is also required to ensur quality of vaccines and, in som stances, has been less than zealo doing so. For 10 years, the DB well as higher government off failed to realize that the division sessed the legal authority to ensu efficacy of vaccines (*Science*, 10 M The confusion that has reigned ov potency of influenza vaccine sin least 1957 is now officially ascrib the DBS to the failure by ma turers to calibrate the colorimeters in assessing the vaccines potenc have taken more than a decade quire that manufacturers stand their measuring instruments is an outstanding record for a regu agency.

Another potency problem oc with typhus vaccine, developed early 1940's and used essentiall changed to immunize all army r at an annual cost of hundreds of ands of dollars. In 1969, the Forces Epidemiological Board that some vaccine lots were not good antibody responses, even they had passed the DBS's potenc It is not known for how many before 1969 the army had been useless vaccine, but the incide some doubt on the general alert the DBS's quality control proc

§ For example, the DBS requires the monkey kidney cells used in growing live polio vaccine to be held for only 28 days in order to ensure that they contain no SV40 virus. According to A. Girardi of the Wistar Institute, SV40 may remain latent for up to 35 days. Nor does the DBS require monkey kidney cells to be screened for chromosomal abnormalities—a possible indicator of cancerous tendencies—a test they would probably fail in large numbers.

logical tests are imprecise, and should not be faulted for having to solve problems that were the prevailing state of the art. Of the DBS's problems with potency tests seem to have much from lack of manage- lack of science.

rview, the various blemishes on escutcheon that have come to recent months are less signifi- the 17-year safety record the behind it. The division was set event recurrence of the 1955 cident and, under Murray's hip none has occurred. Murray isted and outperformed half a mmissioners of the Food and Administration, and many would the belief of the NIH front of- Murray has an excellent record rnment official responsible for a y agency. The chief imperfec- the DBS arise from the nature fice, not its holder. Despite the ss of the federal system for ng vaccines, the major responsi- volves on the DBS, whose director has too much power, too much pressure, and too little protection. There is no limit to the director's term of office and yet no effective mechanism for subjecting his scientific decisions to peer review and peer support. There are conflicting pressures from manufacturers, the scientific community, and, more recently, from the consumer movement. Says one vaccine specialist, "The DBS is the most thankless job in the world—you have to be some kind of a Jesus Christ to do a perfect job. You have to give Murray points for staying power—he hasn't cut and run."

Where Murray has strayed from perfection is probably in taking the narrowmost conception of the division's responsibilities. Safety has been assured, but the improvement of vaccines has been pursued less aggressively. The characteristic posture of the DBS has been one of stand-pat conservatism rather than innovative leadership. A common theme underlying the complaints of critics inside and outside the DBS is Murray's unwillingness to make decisions and even—if the harsher critics are correct—to pursue lines of enquiry that might render necessary a regulatory decision.

Such an attitude is probably inevitable, however, granted the DBS's stretched resources and the belief, presumably endorsed by Murray's superiors, that the DBS should be primarily a rule-making operation with a subordinate and undirected research program. Given these ground rules, it is hard to be sure that anyone else could have bettered Murray's long record in protecting the public from hazardous vaccines.

For the future (Murray is due to retire in 2 years' time), possible changes suggested to *Science* by Turner, Morris, and scientists inside and outside the DBS, include the following proposals. The whole mechanism of biologics control should be reviewed in the light of consumer protection—the DBS should probably assume from the manufacturers the prime responsibility for conducting the more crucial tests of vaccine safety. Preparation should also be made to cope with the surge of new biological products that may be devel-

Briefing

liance for Hearts

n't very long ago at all that Edward M. Kennedy, of Massa- and Representative Paul G. of Florida, were carrying the for opposite sides in the long times bitter tussle ov r who was ge the federal government's against cancer. Apparently the no permanent scars though, the two Democrats say they're orces to back another billion- medical onslaught—this time heart, lung, and circulatory

ews conference held late last a chandeliered room of the uilding, precisely halfway be- e House and Senate wings, nd Kennedy sat shoulder-to- to announce their simultaneous ion of the National Heart, ssel, Lung and Blood Act of bill they both acclaimed as the most important piece of gislation to come before Con- s session.

ill proposes to spend $1.29 billion over the next 3 years on cardiovascular and lung disease, in contrast to current annual funding of $232 million. Under the heading of control programs, $90 million of the new money would go to establish 15 community "screening and education" centers. (The bill doesn't say how these would relate to the Regional Medical Program for heart, cancer, and stroke services run by the Department of Health, Education, and Welfare.) The remaining $1.2 billion would be funneled through the National Heart and Lung Institute to support 15 new clinical R & D centers for cardiovascular disease and 15 new centers for pulmonary disease.

Joint support of the bill by Rogers and Kennedy is especially significant since the two Democrats head the respective House and Senate subcommittees that will handle it. Staff aides for Kennedy and Rogers say the bill's chances of passage are further enhanced by the absence of administrative provisos of the kind that led to last year's contest over the cancer bill.

Approval by Congress, however, may be the least of the heart and lung bill's problems. Even if the appropriation committees grant all the money that the bill authorizes, which is by no means assured, there is no guarantee that the White House will spend it. The Nixon Administration, like its Democratic predecessor, is not in the habit of spending all or even very much of the money Congress generously appropriates for crusades of its own, particularly when those crusades seem designed—if only in part—to overshadow the administration's.

In the present case, the White House seems to be under the impression that the $22 million increase it proposed with some fanfare earlier this year for heart, lung, and blood diseases is generous enough. Congressional Democrats —or at least those on Kennedy's and Roger's subcommittees—disagree. And while their motives may be pure, there is room for suspicion that, by upping the ante nearly an order of magnitude, the Democrats may hope to sink their claws into at least one substantial health issue in an election year when issues of any kind are notably scarce. After all, who's to say that the 790,000 Americans who die from cardiovascular and lung diseases each year are less deserving than the 340,000 who succumb to cancer?—R.G.

oped o[illegible] the next decade. The director of the L[illegible] should have responsibility for organizing the research program as well as the regulatory activities of the division.

In addition, federal responsibility for vaccine development should be clarified, in a way that ensures the DBS does not develop vaccines in-house. There should be some court of appeal against the director's decisions. Since the DBS acts, in effect, for the academic community on behalf of the public, there should be a stronger connection with the academic world than occasional ad hoc conferences and a rubber-stamp board of scientific counselors. Standing committees of scientists might be established—one to oversee research and another for regulations—so as to buttress the director's posture toward manufacturers. Problems with vaccines should be more openly discussed, and herd immunity should be sought by means other than treating the public as one. Most importantly, the boat in which the DBS director sits should be strong and flexible enough to withstand the occasional rocking.—NICHOLAS WADE

APPOINTMENTS

W. G. Bowen

M. H. Bernstein

William G. Bowen, provost, Princeton University, to president of the university. . . . **Marver H. Bernstein**, professor of politics and public affairs, Princeton University, to president, Brandeis University. . . . **David R. Derge**, dean for administration, Indiana University, to president, Southern Illinois Univer[illegible]ty, Carbondale. . . . **Timothy W. Costello**, professor of psychology and management, New York University. . . . **N. Ferbee Taylor**, vice president for administration, Univ[illegible] North Carolina system, to ch[illegible] University of North Carolina, [illegible] Hill. . . . **Ivan L. Frick**, presiden[illegible] Colle[illegible]ge, to president, Elmhurst [illegible] . . . **Harold P. Hanson**, dean, [illegible] School, University of Florida, [illegible] president for academic affairs [illegible] university. . . . **Archie R. Dyk[illegible]** cellor, University of Tennessee, [illegible] to chancellor, University of Te[illegible] Knoxville. . . . **Victor Jones**, [illegible] of engineering and applied physi[illegible] vard University, to dean, [illegible] School at the university. . . . [illegible] G. Cook, assistant professor o[illegible] tion, University of Wisconsin, [illegible] School of Education, Ferris St[illegible] lege. . . . **William Happ**, opera[illegible] search analyst, U.S. Army C[illegible] Engineers, to dean, School of E[illegible] ing, Sacramento State College [illegible] **Leonard E. Goodall**, vice cha[illegible] University of Illinois, Chicago [illegible] to chancellor, University of M[illegible] Dearborn. . . . **Conrad T. Burr**[illegible] fessor of chemical engineering, [illegible] tan College, to dean, School of [illegible] ing at the college.

RESEARCH NEWS

Cancer Radiation Therapy: Potential for High Energy Parti[illegible]

Although the causes of cancer are still unknown, treatment with radiation therapy alone or in combination with chemotherapy and surgery helps to save hundreds of thousands of lives a year. Large doses of radiation, however, damage healthy tissues in addition to destroying tumors and thus may cause severe side effects. The use of high energy particles instead of the conventional x-rays or gamma rays may make possible significant improvements in radiation therapy, according to a growing number of physicists and radiotherapists, and the preliminary results of several laboratory and clinical trials seem to support this belief.

Both the physical and radiobiological properties of energetic particles indicate that they may be able to alleviate some of the problems of conventional radiotherapy, although clinical trials are needed to ascertain that new and untoward effects do not occur. The potential uses of particle radiation may be restricted to localized cancers—a category of diseases that does not include some of the most common, such as lung and breast cancer. Nonetheless, the use of particle radiation, if its potential advantages turn out to be clinically significant, may be able to help the large number of patients who now die from localized cancers despite treatment with conventional radiotherapy.

Practical applications of particle radiation in cancer therapy may be slow in coming. Except on a small scale, the necessary clinical trials are not now being conducted in this country, and there appears to be little likelihood of systematic trials with many types of particles in the near future. Despite the large increases in funding for cancer research, relatively little support is available for radiotherapy research, including particle radiation. National Cancer Institute support for investigations of particle radiation totaled [illegible] $1 million in fiscal year 1971; [illegible] that NCI officials estimate may [illegible] $2.5 million by fiscal 1973. One [illegible] according to NCI, for the relati[illegible] level of funding is a shortage [illegible] fied radiotherapists who are in[illegible] in particle radiation. Research p[illegible] have been rejected by the peer [illegible] system for lack of scientific [illegible] a consequence, according to o[illegible] official, of the naiveté in radiobi[illegible] matters on the part of the p[illegible] who proposed them.

Whatever the reason, several [illegible] laboratories that have an int[illegible] using their particle accelerators [illegible] cer research may find it impos[illegible] do so, and in one case the lack [illegible] sources of funding may result [illegible] closing of the laboratory.

The current interest in medi[illegible] for particle radiation contrasts [illegible] with the attitudes that have p[illegible]

Survey of Childhood Malignancies

ALICE STEWART, M.D., and RENATE BARBER, D.Phil.

IN ITS original form the survey of childhood malignancies conducted by Oxford University included children under 10 years of age who died of cancers or leukemia during the years 1953–55, but it has recently been decided to extend the survey to include deaths since 1955 (table 1). In the final study population there will be children born in 18 consecutive years, 1943–60, whose deaths were spread over 8 calendar years (1953–60). Data collected during the second part of the survey (1956–60 deaths) will differ in several respects from the data on 1953–55 deaths, but the general plan remains the same, and both investigations fall into the broad category of retrospective surveys. All varieties of malignant disease are included and approximately half the deaths are due either to leukemias or to lymphosarcomas. Most of the children will be under 10 years of age at death, but some older deaths may eventually be included in the new population.

The survey of 1953–55 deaths began in October 1956 and was the work of 2 General Register Offices (notifying centers), over 200 local health authority departments (collecting centers), and 1 university department (coordinating center). The same team will be responsible for the survey of 1956–60 deaths, which began in April 1961. In each survey group the original study population included all children in England, Scotland, and Wales who died before their 10th birthday during the survey years.

The authors are with the department of social medicine, Oxford University, Oxford, England. Dr. Stewart is reader in social medicine and Dr. Barber is the holder of the Henry Goodger scholarship for research into blood diseases. *The fieldwork in the study was carried out by county and county borough health departments. The study was aided by grant No. C.5392 from the U.S. Public Health Service. This paper was also published in the Medical Officer, London, January 5, 1962.*

Survey of 1953–55 Deaths

A detailed study of official statistics of mortality preceded the survey of 1953–55 deaths. According to these statistics the risk of dying from a malignant disease after the age of 40 has barely altered in recent years, but the risk of children and young adults dying from these diseases has appreciably increased. In particular, children between 2 and 4 years of age have been more affected by the unfavorable trend of leukemia mortality than any other age group under 70 years (*1*).

These findings suggested that, provided a sufficiently large number of childhood deaths from cancers and leukemias (cases) could be identified and compared, point by point, with suitable controls, there might be a reasonable chance of identifying some of the factors influencing the prevalence of these diseases.

Original aims. Hewitt's critical analysis showed that the recent increase in leukemia deaths happened sooner in technically advanced countries than in other parts of the world and appeared to be more closely related to medical services than to wealth. In Britain the adverse effect of this increase began to be felt at the beginning of the century and received a "postwar fillip"; during the years 1945 to 1953 a striking feature of British and United States statistics was an increase in leukemia deaths in children between 2 and 4 years of age. This was the main reason for deciding to interview mothers of both cases and controls and obtain

firsthand accounts of the children's medical histories and social background. It was also decided that pro formas should include questions about (*a*) illnesses of the mothers and children and X-rays before and after birth; (*b*) treatments with modern drugs; (*c*) living conditions; and (*d*) relatives.

Shortage of cases. Though Britain has a population of 50 million, less than 700 children die of malignant diseases each year. It was necessary, therefore, to plan the survey on a nationwide basis, and to seek the cooperation of public health departments. All county and county borough health departments agreed to take part and to assume responsibility for the fieldwork. Consequently, there were no regional gaps among the 1,640 traced cases, which were originally obtained from 1,973 death certificates supplied by General Register Offices in London and Edinburgh (table 2).

On receipt of the names and addresses of the dead children, the coordinating center sent to each collecting center a list of local cases and the pro formas for recording case and control data. In the larger centers more than one "survey doctor" was appointed, but it was agreed in advance that whoever interviewed the mother of a case should also interview the mother of the corresponding control, also that controls should be obtained from birth registers and not from other sources. To insure uniformity one doctor from the coordinating center briefed all the other doctors and provided them with a written set of instructions.

Selection of controls. The instructions stated that each dead child, or case, was to be paired off with a live child, or control, matched for sex, age, and district, but otherwise picked at random from a local birth register.

The control selection list shows how the control was chosen for a boy (John Smith) who was born in 1952, lived in Sheffield, and died of leukemia in 1958. The names and addresses are imaginary, but other items are genuine.

The names and addresses of five possible controls were obtained from a register of births in the district which included the home address of the dead child. The list indicated the order of priority of selection and included boys born on the same day as the dead child, the next day, and so on. On this occasion the first family selected had moved to an unknown address, but the second was still living at the same address and the mother was willing to be interviewed. She was eventually seen by the doctor who had already interviewed Mrs. Smith.

Table 1. Calendar years of births and deaths of children dying of malignancies, 1953–60, survey of childhood malignancies, Oxford, England

Cohorts		Age at death		Followup period (0–10 consecutive years)	
Births	Deaths	Years	Months	1953–60	1953–55
1943	1953	9–10	108–119	1	1
1944	1953–54	8–10	96–119	2	2
1945	1953–55	7–10	84–119	3	3
1946	1953–56	6–10	72–119	4	3
1947	1953–57	5–10	60–119	5	3
1948	1953–58	4–10	48–119	6	3
1949	1953–59	3–10	36–119	7	3
1950	1953–60	2–10	24–119	8	3
1951	1953–60	1–9	12–119	8	3
1952	1953–60	0–8	0–107	9	3
1953	1953–60	0–7	0– 95	8	3
1954	1954–60	0–6	0– 83	7	2
1955	1955–60	0–5	0– 71	6	1
1956	1956–60	0–4	0– 59	5	0
1957	1957–60	0–3	0– 47	4	0
1958	1958–60	0–2	0– 35	3	0
1959	1959–60	0–1	0– 23	2	0
1960	1960	0	0– 11	1	0

NOTE: In each set of figures, 1 year is incomplete. For example, among the 1960 births children born in January and dying the following December would be only 11 months old.

Table 2. Regional distribution of deaths from malignant diseases in children 0–10 years of age, 1953–55 and 1956–60, survey of childhood malignancies, Oxford, England

Authority	1953–55		1956–60 (original cases)
	Original cases	Traced cases	
Counties:			
Northern England	69	62	118
Midlands	344	290	619
Southern England	711	568	1,191
Scotland [1]	118	89	100
Wales	67	58	125
County boroughs and burghs:			
Northern England	77	70	106
Midlands	307	261	488
Southern England	107	92	192
Scotland [1]	152	134	131
Wales	21	16	27
All local authorities:			
England	1,615	1,343	2,714
Scotland [1]	270	223	231
Wales	88	74	152
All regions	1,973	1,640	3,097

[1] 1956 deaths included with deaths for 1953–55.

The definition of a district varied according to the density of the population and in rural areas often included several villages. If necessary, more than one list of possible controls was compiled, but in the survey of 1953–55 deaths two-thirds of the controls were first choice, and over 90 percent were obtained from a list of five names. Far and away the commonest reason for not obtaining a first choice control was the one shown in the selection control list, namely, that the family had left the district.

In the survey of 1953–55 deaths, if the parents of a dead child had moved to a new local authority area, the rule that a case/control pair should be seen by the same doctor was broken. In the survey of 1956–60 deaths each control will be obtained from the district in which the parents of the corresponding dead child are now residing. In the new survey, therefore, there should be no exceptions to the rule that the same doctor sees each member of a case/control pair. If, however, the proportion of "transfers" is the same as in the original survey, approximately 2 percent of case/control pairs will not be exactly matched for district.

Survey of 1956–60 Deaths

In the interval between the two surveys some facts have been discovered for the first time and others have acquired a new significance:

1. Three independent, retrospective surveys, using different types of controls, have shown a raised incidence of prenatal X-rays among children who subsequently died from malignant diseases (*2–4*).

2. One prospective survey (followup) of children irradiated in utero has shown a raised incidence of harmless somatic mutations (*5*):

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CONTROL SELECTION LIST

For John SMITH Sex M Born on 6.9.52 in Sheffield 3

Priority	Name and address			Selected control (X) [1]
1st	8.9.52	JONES	56 School Lane	D MOVED AWAY
2d	9.9.52	STANLEY	40 Stockport Road	H X
3d	10.9.52	WILLIAMS	5 East Street	H
4th	11.9.52	PETERS	20 Clarke Street	H
5th	11.9.52	HIGGINS	2 Woodside Drive	D

[1] State reasons for not selecting the control of choice (first name on list) or other alternative.

Note: D, domiciliary delivery; H, hospital delivery.

another, concerned only with leukemia deaths, has so far produced negative results (*6*).

3. In 1959 it was discovered that mongolism is due to a chromosomal abnormality which is probably caused by nondisjunction or faulty mitosis during the last reduction division of the gamete (*7*). As a result of this unequal division, mongols carry an extra autosome (No. 21) in all their cells.

4. Though pneumonia is still a common cause of infant deaths among mongols, there have been fewer deaths in recent years (*8*). There are also indications of a substantial increase in the number of mongols dying of leukemia since 1954 (*9*).

5. About 20 percent of mongols have atypical leucocytes (*10, 11*).

6. Hewitt's analysis of leukemia mortality (*1*) covered the period 1930–53. It has since been shown that, in Britain, the peak of leukemia mortality (2–4 years) appeared for the first time in the late 1920's and reached its present height in the mid-1950's (*12*); also, that the pneumonia death rate for children under 5 years began to decline in the late 1920's and reached its present low level in the mid-1950's (*13*).

7. There is a relationship between a child's position in his sibship and his risk of infection, and an exactly opposite relationship between this position and his risk of developing leukemia. Since older children bring infections into their houses, the infection risk is lowest for first-born children and progressively increases as the number of older children increases. Per contra, the leukemia risk is highest for first-born children and progressively decreases as the number of older children increases. Other malignant diseases in childhood do not show this relationship (*14*).

8. Compared with other cancerous children and with healthy controls, the leukemic children in the survey of 1953–55 deaths had a raised incidence of pneumonia and other serious pyogenic infections. The excess was largely due to children who had not been X-rayed in utero and who died before the age of 5 years. These illnesses were exceptionally common among the 19 mongols who died of leukemia, none of whom had been X-rayed before birth.

9. If prenatal irradiation, which usually takes place 7 to 9 months after conception, is a direct cause of leukemia, deaths caused in this way should be directly related, in time, to these exposures. The actual age distribution of such deaths will depend on the incubation period for leukemia, which is not at present known. But unless all childhood leukemias are initiated in the third trimester—an unlikely proposition—it should eventually be possible to demonstrate a difference between the age distribution, at death, of irradiated and nonirradiated cases. A recent study of first-born children in the survey of 1953–55 deaths suggests that leukemias due to prenatal irradiation have a characteristic age distribution, and that these cases die, on the average, 8 months later than nonirradiated cases (*15*). This, in turn, suggests that the vast majority of childhood leukemias are the direct result of events which tend to occur at or near conception.

10. There are several indications that retinoblastomas occur in two forms, one genetically transmitted and one not (*16, 17*).

11. Expectations of cancer in twins are complicated by the fact that twins are more likely than other children to be X-rayed in utero, but in no large series of childhood cancers has there been any indication of an excess of identical cancers among identical twins (*12, 14*). Unpublished results from the survey of 1953–55 deaths suggest that there may in fact be a deficiency of monozygotic twins among cancerous children. In the control group two-thirds of the twins had a twin sib of the same sex. This is the expected proportion, and there were no differences as between the twins who were X-rayed before birth and the other twins. In the case group (children who died of leukemias and cancers) there were 36 twins, 24 of whom had been X-rayed in utero. In this group of 24 X-rayed cases, the expected and observed members of twin sibs of like sex were the same (16). Among the remaining 12 cases not X-rayed before birth, there were only 2 twin sibs of like sex, though the expected number was 8.

The ways in which these and other findings have influenced the design of the 1956–60 survey require some explanation.

Working hypothesis. The natural history of cancers in man might suggest that malignant cells arise de novo and are due to specific, localized changes in the nuclei of somatic cells. But

it is becoming increasingly evident that this is only part of the story.

The Rous theory of co-carcinogenesis (*18*), which is now supported by numerous experiments in animals (*19*), postulates different stages in the formation of a malignant tumor. Normal cells are first converted into "latent cancer cells" by the action of carcinogens or "initiating agents," which produce "hereditable cellular changes" in exposed tissues. This action is irreversible and is followed by a long or short "latent period." Eventually, under the influence of a "promoting agent," the latent cancer cells begin to multiply and form a tumor. According to Berenblum (*20*), promoting agents have the dual action of increasing mitotic frequency and delaying maturation, and the type of cell which can lead to a cancer after being acted upon by an initiator is the comparatively rare kind which normally replenishes tissues; that is, stem cells.

This raises the possibility that cancers in man are due to initiation and subsequent promotion of stem cells. This would include pluripotential cells—ova, spermatozoa, and zygotes—in the category of cells which can develop premalignant properties; so it is necessary to ask why familial cancers and multiple cancers in the same individual are not more common, and why one rarely finds identical cancers in identical twins.

At first sight the absence of twin affinities suggests that there are no genetically transmitted cancers in man other than the obvious ones; namely, retinoblastomas, neurofibromas (Von Recklinghausen's disease) and cancers associated with intestinal polyposis. But the early stages of Von Recklinghausen's disease and intestinal polyposis show that tissues derived from premalignant cells may be at a disadvantage compared with tissues derived from normal cells. It is therefore possible that matching cancers in identical twins are rare, not because germ cells cannot develop premalignant properties, but because a fetus, particularly a twin fetus, derived from a premalignant zygote has a very poor chance of surviving.

If, as a result of initiation, a somatic cell produced a line of cells which were inferior to other cells, the inferior cell line might be eradicated before promotion occurred, thus removing all risk of a cancer developing at the site of initiation. But if, as a result of initiation of a germ cell, a zygote produces a line of inferior premalignant cells, it would usually be impossible for all the cells to be destroyed without causing death. Hence, initiation of a twin zygote might more often produce an abortion than twin cancers.

The few exceptions to the rule that there are no familial cancers are important for two reasons. They show that it is possible for a human zygote to survive a premalignant change, and they suggest that this change is due to a single gene substitution or point mutation. If a premalignant state merely reflected a general change in the cytoplasm, or a change which affected the nucleus as a whole, one would expect a premalignant change in a pluripotential cell to produce multiple cancers more often than not. In practice, familial cancers tend to be confined to certain cell types and to organs which are less likely to cause death, if wholly composed of inferior cells, than to other parts of the body.

Nevertheless, a point mutation in a somatic cell or germ cell might be preceded by changes in the cytoplasm and accompanied by other changes in other genes. For instance, a change in the cytoplasm might cause faulty mitosis the next time the cell divided: on one occasion faulty division of the nucleus might involve only one gene, on another occasion, several genes on the same chromosome, and on yet another occasion, several genes in several chromosomes. The risk of immediate death of the cell would be proportional to the number of genes involved, and it is unlikely that any cell would survive an accident which involved more than one chromosome. If, however, the cell survived faulty division of one chromosome, all that would matter, from the point of view of the subsequent development of a cancer, would be whether or not a gene controlling the nature of specific daughter cells had undergone a premalignant change.

If a mitotic aberration happened during formation of a somatic cell and the cell survived, the remote effects of a change in several genes on the same chromosome—deletion, duplication, translocation, or inversion—might be the same as a change in only one gene. But if the

faulty mitosis happened during formation of a germ cell or zygote, that is, a pluripotential cell, all the genes involved in the accident would influence the end result. A fetus possessing only one inferior, premalignant cell system might survive to produce a child who appeared to be normal at birth and subsequently developed malignant changes in the defective tissues: but a fetus possessing several abnormal cell systems would probably die in utero. Even if the pregnancy terminated in a live birth, the child would have several congenital defects and would be unlikely to survive long enough to develop a cancer.

So far as we know, the only congenital disease due to involvement of an autosome in a mitotic aberration which is both common and compatible with several years of life is mongolism. Mongolism, or trisomy of chromosome No. 21, is also the only congenital disease which is consistently associated with one type of malignant disease, namely leukemia: and this association was not discovered until the life expectancy of mongols increased from less than 2 years to over 14 years. Before the discovery of antibiotics, mongols usually died of pneumonia during infancy, and there is no doubt that a low resistance to bacterial infections is part of the mongoloid syndrome. Hence it is reasonable to suggest that one of the genes controlling leukopoiesis is situated on chromosome No. 21, which is also one of the smallest autosomes.

The size of a chromosome sets a limit to the number of genes which can be damaged during mitosis. There should therefore be a correlation between the size of a chromosome and the number of times that faulty division of the said chromosome causes death of the cell. In this way the position of an important leukopoietic gene might influence the prevalence of childhood leukemias. But before developing this theme it is necessary to consider what effects a "preleukemic change" in a germ cell might have and how these would compare with the effects of a similar change in a somatic stem cell (leukocyte precursor).

According to the theory outlined above, a preleukemic change in a germ cell would probably involve several genes on the same chromosome and would in any case impair the efficiency of all circulating leukocytes. Consequently, if the fetus survived, the risk of an infection death during infancy would be exceptionally high, and only children who escaped these early deaths would die of leukemia. Moreover, any reduction in infant mortality, due either to prevention or cure of infections, would adversely affect the leukemia death rate (*1* and chart).

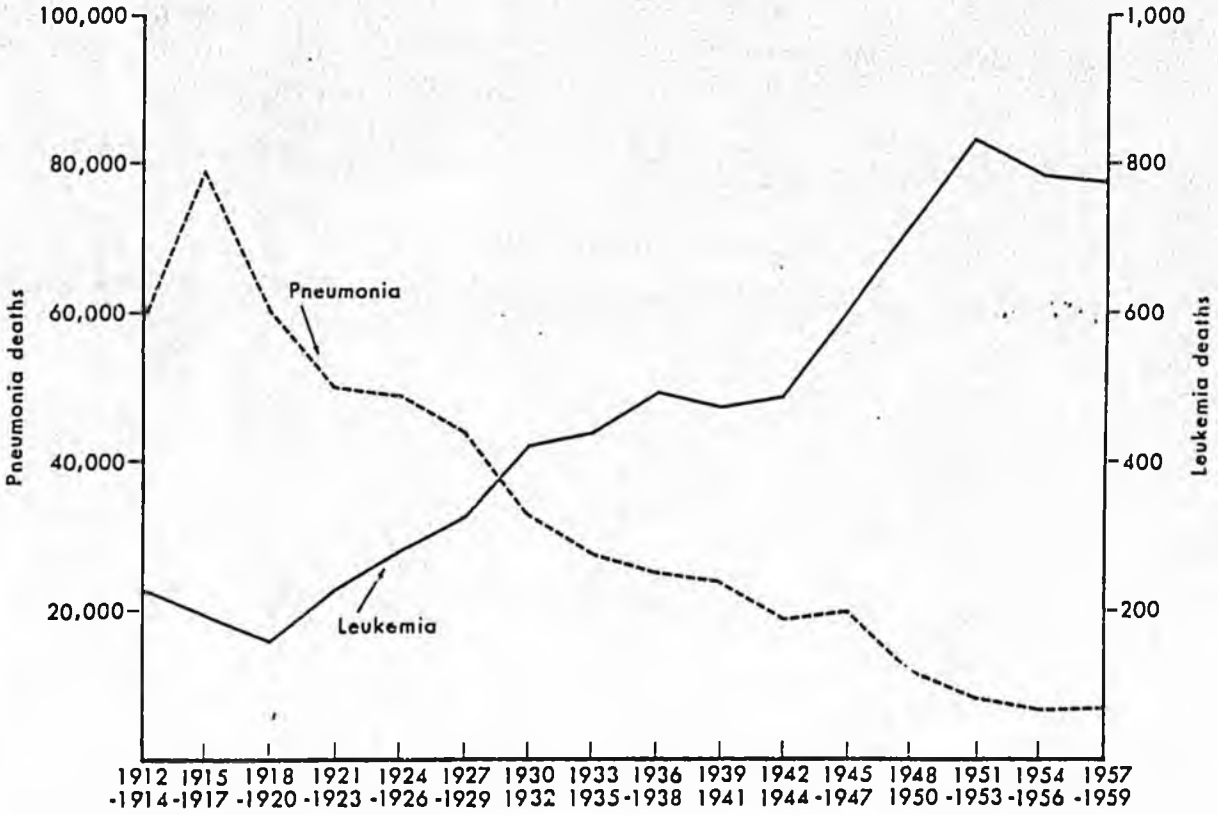
Premalignant conditioning of a leukocyte precursor in an adult, that is, a somatic cell, would also impair the efficiency of daughter cells, but in such cases the existence of healthy leukocytes derived from normal stem cells would provide some protection against infections. Consequently the risk of an intercurrent death should be comparatively small, and to produce an adverse effect on the leukemia death rate there might have to be a substantial decrease in the infection death rate.

Finally, if it is possible for faulty mitosis during the formation of a germ cell to impair the efficiency of leukocytes, and to pave the way for subsequent malignant changes in leukocyte precursors, one would nowadays expect a retrospective survey to reveal a raised incidence of potentially lethal infections among children who subsequently developed leukemia, provided that antibiotics were easily accessible.

In the 1958 report of the survey of 1953–55 deaths from cancer and leukemia (*2*), a raised incidence of pneumonia among the children who subsequently died of leukemia was mentioned. But the possibility that this finding was important and related to the high incidence of mongolism was not considered until 1959, when the origins of mongolism were explained for the first time. Once it was realized that mongolism was due to a chromosomal abnormality which had been present since conception and which predisposed not only to infections but also to malignant changes in the cells which protect the body against infections, the possibility that other cases of leukemia and cancer in childhood were due to lesions which predated or coincided with conception had to be considered.

Reexamination of the data on 1953–55 deaths from cancer and leukemia (*9*) showed that pneumonia was the commonest, but not the only potentially lethal, infection which was

Deaths from leukemia and pneumonia in children 0–10 years of age, England and Wales, 1912–59, by 3-year periods



recorded more often in the medical histories of children who subsequently died of leukemia than in the histories of children who subsequently died of other cancers. Since a raised incidence of these serious infections was a striking feature of mongols and other children who died of leukemia before the age of 5 years and were not X-rayed in utero, it was suggested that there might be two distinct varieties of leukemia in childhood: one initiated at or before conception and associated with a low resistance to infection (common form) and the other initiated in utero or after birth and associated with a normal resistance to infection (rare form).

The family histories of the survey children were scrutinized for evidence of a raised incidence of nonmalignant blood diseases in the relations of leukemic children. The data proved inadequate for this purpose but they did succeed in showing that, despite their rarity, "cancer fraternities," that is, the same malignant disease affecting more than one member of a sibship, were more common than would be expected if they were merely chance phenomena.

There were other indications in the original data that genetically transmitted cancers were not confined to retinoblastomas, but it was not possible to be certain that this was so. Hence the decision to extend the survey and redesign the pro formas so that there would be some possibility of testing the theory that faulty mitosis during or before zygote formation is a common cause of malignant disease in childhood, though these diseases may also be due to mitotic aberrations involving somatic cells. It was also hoped that the new data would help to settle the controversy about prenatal X-rays being a cause of malignant disease in childhood.

This controversy exists because it is impossible to be certain that, in the retrospective surveys mentioned above, the normal incidence of prenatal X-rays was correctly estimated. It is therefore important to obtain evidence which is independent of control data. If all children born in a given period who subsequently died

of malignant disease could be traced, it would be a relatively simple matter to decide whether "irradiated" and "nonirradiated" cases had different age distributions. The survey of 1956–60 deaths will not provide all the facts required, but if it is successful, the data will include an 8-year followup of children born between 1950 and 1953 and may be sufficient for the purpose (table 1).

Other theoretical considerations. The suggested working hypothesis would only be acceptable if it offered a rational explanation of the following facts. First, infants apart, the risk of developing a malignant disease decreases with age before puberty and increases with age after puberty. The age distribution of children with cancers, that is, the age at death, varies with cell type. Cancers of nervous tissues are commonest in the first and second years, renal cancers and retinoblastomas in the third year, leukemias in the fourth year, and lymphosarcomas in the fifth year. Second, compared with other cancers, leukemias have always been relatively common in childhood and are nowadays the commonest variety of malignant disease in childhood. In adults less than 10 percent of malignant diseases are leukemias.

Age distribution. So far nothing has been said about the nature of "promoters" except that there is reason to think that in normal circumstances they do no harm, and merely encourage mitosis. Since it is only in the presence of premalignant cells that a promoter ever produces a cancer, it is possible that "natural promoters" include growth factors (general promoters) and also repair mechanisms and defense mechanisms (local promoters). Assuming that this is so, and that there is a sizable population of premalignant genes in newly formed zygotes, one would expect the risk of promotion during childhood to decrease with age (general promoters) and the risk during adult life to increase with age (local promoters). One would also expect a temporary increase in risk during puberty, but this would be difficult to detect in national statistics because these only show deaths in 5-year age groups. Lee (*21*), who obtained deaths for individual years, has shown that there is a temporary increase in the leukemia death rate during adolescence. Since malignant cells are incapable of maturing much beyond the stage which they have already reached, one would also expect to find that, when promotion occurred within a few weeks of conception, the resulting tumor contained less well differentiated cells than when promotion occurred later. One purpose of the survey is to discover whether there is any correlation between age at the onset of the fatal disease and the maturation phase of the cancer cells.

Preponderance of leukemias. It has already been suggested that the small size of chromosome No. 21 may be related to the fact that leukemia is a relatively common variety of cancer in childhood. According to this theory a gene controlling leukopoiesis should be situated on chromosome No. 21, and leukemia might be the result of this chromosome being involved in a mitotic aberration.

Provided a preleukemic state was the result of faulty mitosis in a leukocyte precursor, that is, in a somatic cell, there might be no obvious side effects due to involvement of other genes on the same chromosome. But if the change affected a germ cell there would be important side effects if neighboring genes were damaged. There are fewer genes at risk in chromosome No. 21 than in other autosomes, and in view of what is now known about mongolism, these genes may be less essential for vital processes than genes on other chromosomes.

The statistical association between mongolism and leukemia was one reason for postulating a leukopoietic gene on chromosome No. 21. Another reason is the so-called Philadelphia chromosome. This is the name which has been given to an abnormality which has been found in the leukocytes of some, but not all, cases of myeloid leukemia in adults (*22*). The chromosome involved is either No. 21 or No. 22, which are difficult to distinguish, and its appearance suggests that during division of a leukocyte stem cell part of the chromosome was lost.

According to the theory outlined above, there would be nothing paradoxical about finding a partial deletion of a chromosome in some cases of leukemia, and a duplication (trisomy) of the same chromosome in other cases. Nor would it be surprising to discover that when the chromosomal abnormality is found in all cells, the leukemia occurs early and is accompanied by

other congenital defects, and when it is found only in leukocytes, the leukemia occurs late, and there are no congenital defects.

Another feature which has probably influenced the prevalence of leukemias in childhood has already been mentioned: namely, the lowering of the infant mortality rate. Thirty years ago cancers of nervous tissues, that is, neuroblastomas and cerebral tumors, more often caused death in childhood than leukemias, and it is only since the discovery of sulfonamides that leukemias have taken first place.

Progress. With these ideas in mind the second part of the survey was launched in April 1961. Once again county and county borough health departments have assumed responsibility for the fieldwork and already arrangements have been made to trace more than three-quarters of the children who died between 1956 and 1960 (table 2). As in the survey of 1953–55 deaths, each dead child will be paired off with a live child of the same age and sex, and doctors will interview mothers. The mothers' descriptions of their children's illnesses, X-ray exposures, and family histories will be recorded on specially printed schedules and the more important items will be checked with hospital records.

Pedigree data. In the survey of 1953–55 deaths some information about the mother's relatives was obtained, but comparatively little attention was paid to the father and his side of the family. Mothers were asked if they knew of any relatives who had died of cancer or leukemia, but their answers showed that they knew, offhand, less about their husbands' relatives than about their own. In the survey of 1956–60 deaths more extensive family histories will be recorded and a new method of collecting pedigree data has been devised.

Each mother will be visited first by a health visitor assigned to her parish. The health visitor's instructions are: (*a*) to obtain the cooperation of the mother; (*b*) to ascertain the date of birth of the dead child (this is needed to obtain the control); (*c*) to explain what is required; and (*d*) if necessary to help the parents to complete schedule X, Enumeration of Relatives.

In general, schedule X will be given to the mother about a week before the doctor calls, together with a covering letter which asks her to record, under printed headings, all that she and her husband know about "the four grandparents of the survey child and all their direct descendants, including stillbirths and miscarriages." The printed headings include position in sibship, illnesses and X-ray experiences (parents), all causes of death and other specified illnesses (other relatives), dates of birth and present state of health or cause of death (sibs), miscarriages and stillbirths (mothers and grandmothers).

Control selection lists. Schedule X is an example of an innovation made in the light of earlier experiences. Another example is the entry alongside each name on the Control Selection List of the letter D (domiciliary delivery) or H (hospital or nursing home delivery). Knowing as we now do that the cases in the survey of 1953–55 deaths had a higher incidence of prenatal X-rays than the controls (*2*), it is clearly important to know whether first choice controls are representative of the population at large in respect of birthplace: also whether failure to obtain 100 percent of first choices has biased the control group in this respect.

Other sources of bias. Retrospective data collected by several doctors direct from mothers of living and dead children are subject both to recording bias (doctors) and to reporting bias (mothers). By insisting from the beginning that the records from each case/control pair be compiled by one doctor, the first type of bias should have affected case and control data equally, and should not have been an important source of error in the earlier reports (*2*, *9*). It is less certain that the second source of error has not affected these reports, and the suspicion still remains that the findings in respect of prenatal X-rays were due to "memory bias" (*23*).

A knowledge of the ways in which the original case and control groups differed from one another should make it possible to collect more convincing data in the new survey. On this occasion answers to questions which are expected to reveal differences between cases and controls will be systematically checked. In addition, several new questions will be asked for the express purpose of discovering whether events which could not possibly have affected

the children, for example, X-rays of the parents after birth of the child, are reported with equal frequency by parents of both cases and controls. In the original survey only positive statements about abdominal X-rays during pregnancy were confirmed by asking X-ray departments to produce the original records. In the survey of 1956–60 deaths addresses of antenatal clinics and X-ray departments will be automatically recorded, and the intention is to check negative statements about X-rays on a sample basis, and positive statements on a comprehensive basis.

Checking records. As soon as the completed pro formas are returned to Oxford they are examined to see if they are internally consistent and to decide what type of postal followup is required. The object of this is to obtain hospital records of the fatal illness and confirmatory evidence about the following statements:

- X-rays and illnesses of the mother during the pregnancy of the survey child, including anemias and threatened abortions.
- Relatives with anemia or other blood diseases, including leukemias.
- Relatives with "matching" cancers: that is, the same type of cancer as the "index" case.
- Relatives said to have died at an early age from an obscure cause.

In addition, approximately 25 percent of negative statements about X-rays and other antenatal events will be checked by asking antenatal clinics to make an abstract of the original notes on a specially printed form (schedule G). If necessary, more information will be obtained from the mothers, and some parents will be asked if they are willing to have sibs of the survey child examined. Twins will be included in this group; also children who have lost more than one sib, or have two or more relatives with blood diseases: for example, leukemia, pernicious anemia, purpura, acholuric jaundice, and aplastic anemia.

Present status. At the time of writing (September 1961), 220 case/control pairs have been completed and 85 "lost" cases have been returned to Oxford. The proportion of lost cases is high, but this is not surprising since it takes longer to complete the records for a case/control than to discover that a family has moved to an unknown address (49 cases), or that the mother is either not willing to cooperate (30 cases), or not in a fit state to be interviewed (6 cases). Already a considerable amount of information about the lost cases has been obtained from other sources, such as hospitals, welfare clinics and schools, and in two cases this was sufficient to justify finding a "matched" control.

The results of the postal followup suggest that the numbers of X-ray records which are still available are larger than the numbers which have been destroyed and may be sufficient to test the accuracy of the mothers' statements. There has been no difficulty in obtaining from hospitals either the original records of the fatal illnesses or abstracts of the original notes on specially printed forms (schedule A). So far none of the mothers who have been interviewed has resented a followup letter and most of them have been able to complete schedule X. We feel confident that, provided they are given sufficient time, the parents of our survey children will be able both to enumerate their relatives and to tell us where to look for hospital records and death certificates. It is too soon to say how many of the children who died between 1956 and 1960 will eventually be traced, but the prospects are at least as promising as they were at the same stage of the survey of 1953–55 deaths.

Summary

The survey of childhood malignancies originally included only children who died between 1953 and 1955 but has recently been extended to include later deaths. In the final study population there will be children who were born in the 18 consecutive years 1943–60 and whose deaths were spread over the 8 calendar years 1953–60.

The method of collecting data and selecting controls for the 1953–60 deaths remains the same, but the pro formas have been revised and there will be more systematic checking of mothers' statements against hospital records.

It is hoped to settle the controversy about the effects of prenatal X-rays by comparing the ages of irradiated and nonirradiated children, and thus obviate the need to place reliance on control data.

It is suggested that the first stage in cancer promotion is a mitotic aberration and that the

commonest cause of childhood cancers is faulty mitosis during division of a germ cell. Following such an accident the risk of death before a tumor has time to develop is much higher than the corresponding risk following faulty mitosis in a somatic stem cell. Consequently there are no "twin affinities" and there is a low incidence of familial cancers.

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Radiation Symposium

A symposium on the technological needs for reduction of patient exposure from diagnostic radiology will be held March 5–6, 1962, in the main auditorium of the Health, Education, and Welfare Building, Washington, D.C. The symposium, sponsored by the Public Health Service, will evaluate present knowledge and discuss future investigation in four main categories: human and phantom dosimeters; radiographic equipment; fluoroscopic and intensifier equipment; and radiographic grids, screens, and films.

For further information and tickets, contact Dr. M. L. Janower, Division of Radiological Health, Public Health Service, Washington 25, D.C.

of such controls in experiments concerned with the role of oncogenic transformation *in vitro* by known agents.

With the recognition of the S antigen the question arose concerning its relationship to the SV40 tumor-homotransplantation antigen of Habel and Eddy (1963) because of its orientation at the cell surface where, presumably, the Habel antigen is also located. The materials provided by the present series of experiments appear to offer means of investigating this problem experimentally by comparing the oncogenic titer of cells from S-positive, T-negative lines with the titer of homologous oncogenic nonexposed lines in SV40-immunized hamsters according to Habel's technique (1962). Experiments of this kind are in progress.

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Differential Bacteriophage DNA Replication after Induction of a Strain of *Escherichia coli* Doubly Lysogenic for φ80 and φ80dlac

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A double lysogen of *Escherichia coli* containing prophages φ80 and φ80dlac (with a temperature-sensitive repressor for phage induction) has been investigated for yields of the two bacteriophages under different conditions of growth and lysis. The yield of φ80dlac is strongly dependent on the growth medium used. In growth medium A approximately equal amounts of φ80 and φ80dlac are obtained. In growth medium B a reasonable yield of φ80 is produced but very little φ80dlac is produced. This is due to the fact that very little φ80dlac DNA is produced in an induced culture in medium B. A minor modification of Campbell's model for prophage excision is suggested in which homologous parts of the two prophages interact to form one intact phage chromosome. If this mechanism of excision prevailed in medium B it could account for the low yield of transducing phage.

INTRODUCTION

The factors controlling the induction of temperate bacteriophages are the subject of much current investigation. In order for induction to occur, a cytoplasmic repressor encoded by the prophage must be destroyed. According to recent studies (Weisberg and Gallant, 1968) protein synthesis is necessary in order for the detachment of the prophage λ to occur after the repressor is destroyed. The work of Signer and Beckwith (1966) suggests that in the related virus φ80 this may involve the synthesis of enzymes which specifically promote recombination in the phage attachment site region and therefore may be responsible for phage detachment.

This paper is concerned with a doubly lysogenic strain of *E. coli* containing φ80 and φ80dlac as prophages. The φ80dlac was derived from the φ80 particle in the manner described by Signer and Beckwith (1966). According to the Campbell (1962) model for the formation of a transducing phage, both prophages should contain similar attachment sites for the bacterial chromosome. The two phages should in fact be isogenic except for the region containing the transducing fragment. Because of this, one would expect induction and replication of both prophages in the double lysogen should be subject to the same control factors. In the course of attempting to optimize phage yield it has been observed, contrary to expectation, that the *relative* amounts of the two prophages are subject to large variations dependent on growth conditions. A description of our most striking findings is contained herein.

MATERIALS AND METHODS

Media

Medium A: LB broth, per 1 liter distilled water; bactotryptone (Difco), 10g; yeast extract, 5 g; NaCl, 10 g; 20% glucose, 5 ml; and 1 *M* $CaCl_2$, 2.5 ml added after autoclaving.

Medium B: per 1 liter distilled water: KH_2PO_4 (anhydrous), 5.6 g; K_2HPO_4 (anhydrous) 28.9 g; yeast extract, 10 g; thiamine, 10–15 mg; and 25% glucose 40 ml added after autoclaving.

L-broth: per 1 liter distilled water: bactotryptone (Difco), 10 g; yeast extract, 5 g; NaCl, 5 g; 5 ml 20% glucose, 5 ml; and

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Development of S and T Antigens and Oncogenicity in Hamster Embryonic Cell Lines Exposed to SV40[1]

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Cultures of 7 nononcogenic lines of Syrian hamster cells originating from the same pool of embryonic tissues were exposed to SV40. Four months later tests for "Surface" (S) and "Tumor" (T) antigens and for oncogenicity were performed on cells deriving from these cultures and on cells from homologous unexposed cultures which were maintained under the same conditions. Cells from 4 of the virus-exposed lines exhibited S antigen, and 2 of these also exhibited T antigen. Neither antigen was detected in cells from unexposed cultures. Among cells from exposed cultures only those exhibiting one or both of the antigens were found to induce tumors in hamsters. Among those from unexposed cultures, 2 had clearly become oncogenic. The latter were homologous with the virus-exposed cultures which exhibited S antigen only. Results of tests for S and T antigens on the cells of tumors resulting from implantation of exposed and unexposed cells revealed an exact qualitative correlation between the distribution of these antigens in the tumor cells and in the homologous cells prior to implantation. The proportion, however, of T-positive cells which was low in the cultures before implantation was found to approach 100% in the homologous tumor cells.

In general the results provide evidence that the synthesis of S antigen is specifically determined by the SV40 genome and may take place independently of the synthesis of T antigen. Because of concurrent "spontaneous" oncogenic transformation in homologous cultures not exposed to SV40, no association between the capacity to synthesize S antigen and the development of oncogenic potential was established.

INTRODUCTION

Oncogenic transformation not associated with the development of "tumor" (T) antigen in hamster[3] lung and liver cells exposed to simian virus 40 (SV40) has been described by Diamandopoulos and Enders (1965). In another series of experiments van der Noordaa and Enders (1966) failed to detect T antigen in primary cultures of newborn hamster lung cells during a period of 8 weeks after exposure to SV40. Because of lack of direct evidence it was impossible at that time to decide whether transformation was associated with persistence of the viral genome or represented spontaneous acquisition of oncogenicity. Recognition of "surface" (S) antigen by Tevethia and his coworkers (Tevethia and Rapp, 1965; Tevethia *et al.*, 1965) in SV40-transformed cells ap-

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[3] Throughout "hamster" refers to golden Syrian hamster.

peared to offer means whereby this problem might be further investigated. Accordingly, tests for S antigen were done and found to be positive in 3 of the 6 lung cell lines and 1 of the 5 liver cell lines to which we have just referred. S antigen, although not consistently associated with oncogenic potential in the liver lines was clearly detected only in lung lines that were oncogenic (unpublished observations). These findings suggested that in the lines synthesizing S antigen the SV40 genome might be present but possibly in a more repressed or incomplete state, since synthesis of T antigen was not observed.

To obtain further relevant data, the experiments described here were undertaken in which established lines of "normal" hamster embryonic cells were employed. These lines were selected because they permitted the simultaneous study of uninoculated control cultures, which were comparable in all other known respects to those exposed to the virus. The procedure adopted was basically analogous to that employed in experiments with the lung and liver systems (Diamandopoulos and Enders, 1965), i.e. the virus was added and the cultures were allowed to remain without cell transfer for a period of 3 months when cell passages were resumed.

MATERIALS AND METHODS

Virus. SV40, strain VA 45-54, was grown in monolayer cultures of line AH-1 Grivet monkey kidney cells (Günalp, 1965). $TCID_{50}$ 0.1 ml as determined in this system was log 6.2.

Cells. (a) Hamster embryo cell lines. Seven uncloned lines, all of which originated from the same pool of hamster embryonic tissues (Diamandopoulos and Enders, 1966) were employed. Cells were grown in Puck's medium with addition of 10% inactivated horse serum and 10% fetal calf serum. When tested for oncogenicity (Diamandopoulos and Enders, 1966) at the 15th and 30th passages (10 and 15 months, respectively, after initiation), none of these lines produced tumors after subepithelial implantation of 10^6 cells into the Syrian hamster cheek pouch. As routine, passages were carried out at weekly intervals. At the 30th passage level aliquots of cells of each line were frozen and stored. After 6 months the cells were quickly thawed at 37°C and propagated according to procedures previously described (Diamandopoulos and Enders, 1966). (b) Monkey cells. Cultures of the AH-1 line of grivet monkey kidney cells (Günalp, 1965) were grown in monolayers employing Puck's medium containing 10% inactivated horse serum and 10% fetal calf serum.

Tests of oncogenicity. Cell suspensions were prepared, enumerated, and implanted subepithelially in aliquots of 0.5 ml containing 10^6 cells, into both cheek pouches of weanling male Syrian hamsters, according to procedures already described (Diamandopoulos and Enders, 1966). As routine, 6 animals were used for each cell suspension tested.

Immunofluorescence techniques. (a) Tests for T antigen were performed by the indirect fluorescence antibody technique as previously described (Diamandopoulos and Enders, 1965). (b) Tests for S antigen were carried out by the indirect immunofluorescence antibody technique originally described by Möller (1961). Briefly, the cells growing in tissue culture as monolayers were brought into suspension with 0.3% trypsin, washed once with Eagle's medium containing 10% fetal calf serum and 3 times with Tris-buffered saline (TBS), pH 7.4. After the final wash, 10^6 cells were allowed to react with 4 drops of serum from SV40-vaccinated hamsters that had resisted transplantation of 100,000 hamster cells transformed by SV40. After incubation for 1 hour at 37°, the cells were washed 3 times with TBS and were allowed to react with antihamster γ-globulin horse γ-globulin conjugated with fluorescein isothiocyanate. After incubation for 30 minutes at 37° in the dark, the cells were washed 3 times, drained, suspended in buffered glycerol (pH 7.0), and examined in a Zeiss fluorescence microscope. Only the cells showing a bright green fluorescence in the form of a ring around the cell were counted as positive. A cell line was called positive for S antigen only if more than 50% of the cells showed specific membrane fluorescence. Controls included either the normal hamster serum or serum from adenovirus type 12 tumor-bearing hamsters allowed to react with the cells under test. Cells known to contain SV40 specific S antigens were also included in each test. The preparation of S antibody and the numerous tests carried out to demonstrate the specificity of the reaction are described elsewhere (Trevethia *et al.*, 1965, 1967).

TABLE 1

TESTS FOR ONCOGENICITY AND THE DEVELOPMENT OF S AND T ANTIGENS IN 7 LINES OF HAMSTER EMBRYONIC CELLS EXPOSED AND NONEXPOSED TO SV40

Lines	Oncogenicity	"S" Antigen[a]		"T" Antigen[a]		Oncogenicity[a]		Tumor Cell "S"		Tumor Cell "T"		Serum "Anti-T"	
	10 and 15 Months	4 months		4 months		4 months		3 months		3 months		3 months	
	Non-SV40 Exposed	SV40 Exp.	Non-Exp.	SV40 Exp.	Non-Exp.	SV40 Exp.	Non-Exp.	SV40 Exp.	Non-Exp.	SV40 Exp.	Non-Exp.	SV40 Exp.	Non-Exp.
E	–	+	–	–	–	+	+	+	–	–	–	–	–
P	–	+	–	–	–	+	+	+	–	–	–	–	–
M	–	+	–	1-3% +	–	+	–	+		100% +		+	
2Ps	–	+	–	0-1% +	–	+	–	+		100% +		+	
Ks	–	–	–	–	–	–	–						
Ps	–	–	–	–	–	–	–						
I	–	–	–	–	–	–	±						

[a] Lines were frozen for six months, then thawed for experiment. S = surface, and T = tumor, antigens.

RESULTS

Two monolayer cultures of each of the 7 nononcogenic hamster embryonic cells lines in the 32nd passage were prepared in test tubes (16 × 150 mm). At the same time and employing the same cell suspensions, 4 cultures of each line were prepared on coverslips carried in Leighton tubes. On day 3 after the cultures were established, 0.1 ml of undiluted stock SV40 was added to one of each of the 2 test tube cultures and to 2 of each of the 4 Leighton tube cultures of each cell line. In addition, 0.1 ml of stock virus was added to each of 2 coverslip cultures of the AH-1 line of grivet monkey kidney cells in Leighton tubes. Comparable uninoculated cultures of monkey kidney cells were included as controls. All cultures were then incubated at 37°. At 24 and 48 hours after addition of SV40, cover glasses were removed from inoculated and uninoculated Leighton tube cultures and the cells were examined for presence of T antigen by the indirect immunofluorescence technique. A majority of the SV40 exposed grivet monkey cells showed after 24 hours typical intranuclear fluorescent staining and the numbers of such cells had increased by 48 hours. Specific fluorescence was not seen in uninoculated monkey cell preparations, nor in any of the SV40-exposed or unexposed hamster cell cultures.

The remaining 7 SV40-exposed hamster cell test tube cultures with their 7 unexposed homologous cultures were subsequently maintained for 3 months with twice weekly changes of growth medium but without subculture. Frequent microscopic examination gave the impression that the cell populations in the virus-exposed cultures increased slightly as compared with those in the unexposed group. At the end of the 3 month period, 4 successive passages at weekly intervals of the cells from each of the 14 cultures were made, dividing the cells by one half at each passage. Cultures of the 4th passage were tested for presence of S and T antigens, for plating efficiency, and for oncogenic potential. The results of the tests for these antigens and for oncogenicity are summarized in Table 1. Plating efficiencies, since they failed to show any significant differences between SV40-exposed and un-

of such controls in experiments concerned with the role of oncogenic transformation *in vitro* by known agents.

With the recognition of the S antigen the question arose concerning its relationship to the SV40 tumor homotransplantation antigen of Habel and Eddy (1963) because of its orientation at the cell surface where, presumably, the Habel antigen is also located. The materials provided by the present series of experiments appear to offer means of investigating this problem experimentally by comparing the oncogenic titer of cells from S-positive, T-negative lines with the titer of homologous oncogenic nonexposed lines in SV40-immunized hamsters according to Habel's technique (1962). Experiments of this kind are in progress.

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Differential Bacteriophage DNA Replication after Induction of a Strain of *Escherichia coli* Doubly Lysogenic for φ80 and φ80dlac

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A double lysogen of *Escherichia coli* containing prophages φ80 and φ80dlac (with a temperature-sensitive repressor for phage induction) has been investigated for yields of the two bacteriophages under different conditions of growth and lysis. The yield of φ80dlac is strongly dependent on the growth medium used. In growth medium A approximately equal amounts of φ80 and φ80dlac are obtained. In growth medium B a reasonable yield of φ80 is produced but very little φ80dlac is produced. This is due to the fact that very little φ80dlac DNA is produced in an induced culture in medium B. A minor modification of Campbell's model for prophage excision is suggested in which homologous parts of the two prophages interact to form one intact phage chromosome. If this mechanism of excision prevailed in medium B it could account for the low yield of transducing phage.

INTRODUCTION

The factors controlling the induction of temperate bacteriophages are the subject of much current investigation. In order for induction to occur, a cytoplasmic repressor encoded by the prophage must be destroyed. According to recent studies (Weisberg and Gallant, 1968) protein synthesis is necessary in order for the detachment of the prophage λ to occur after the repressor is destroyed. The work of Signer and Beckwith (1966) suggests that in the related virus φ80 this may involve the synthesis of enzymes which specifically promote recombination in the phage attachment site region and therefore may be responsible for phage detachment.

This paper is concerned with a doubly lysogenic strain of *E. coli* containing φ80 and φ80dlac as prophages. The φ80dlac was derived from the φ80 particle in the manner described by Signer and Beckwith (1966). According to the Campbell (1962) model for the formation of a transducing phage, both prophages should contain similar attachment sites for the bacterial chromosome. The two phages should in fact be isogenic except for the region containing the transducing fragment. Because of this, one would expect induction and replication of both prophages in the double lysogen should be subject to the same control factors. In the course of attempting to optimize phage yield it has been observed, contrary to expectation, that the *relative* amounts of the two prophages are subject to large variations dependent on growth conditions. A description of our most striking findings is contained herein.

MATERIALS AND METHODS

Media

Medium A: LB broth, per 1 liter distilled water; bactotryptone (Difco), 10g; yeast extract, 5 g; NaCl, 10 g; 20% glucose, 5 ml; and 1 *M* $CaCl_2$, 2.5 ml added after autoclaving.

Medium B: per 1 liter distilled water: KH_2PO_4 (anhydrous), 5.6 g; K_2HPO_4 (anhydrous) 28.9 g; yeast extract, 10 g; thiamine, 10–15 mg; and 25% glucose 40 ml added after autoclaving.

L-broth: per 1 liter distilled water: bactotryptone (Difco), 10 g; yeast extract, 5 g; NaCl, 5 g; 5 ml 20% glucose, 5 ml; and

exposed cells, are not presented. From Table 1 it is apparent that in all the uninoculated cultures neither S nor T antigen was demonstrated. Cells from 3 of the SV40-exposed cultures also failed to synthesize these antigens (Ks,Ps,I). Cells of the 4 remaining cultures that were exposed initially to SV40 developed S antigen (E, P, M, 2Ps), and in 2 of these (M, 2Ps), cells synthesizing T antigen were also found. It is of interest that in these two lines the proportion of T antigen-positive cells was low. That this low ratio of T positive to T negative cells was maintained *in vitro* was shown by examination of cultures of the same lines which were subjected to 2 additional passages.

Tests for oncogenicity demonstrated that cells of 2 of the uninoculated lines (E and P) acquired this property during the course of the experiment since progressively growing tumors developed in both cheek pouches of all hamsters into which they were implanted. Uninoculated line I probably became weakly oncogenic, since a single small tumor (3 mm) developed in one of the 6 hamsters, each of which received 10^6 cells. Among the SV40-exposed lines, 4 became oncogenic (E, P, M, 2Ps) as indicated by rapid and vigorous growth of the tumor masses in all animals tested. The pathogenesis and morphologic manifestations of these tumors as compared with those induced by cells of uninoculated lines will be described elsewhere.

To determine whether the cells of tumors induced by cell lines remained unchanged in respect to the synthesis of S and T antigens, tumor tissues were trypsinized and cell suspensions thus obtained were grown as monolayers and examined in the first passage by the immunofluorescence technique. These results are also summarized in Table 1. It is evident that correlation was complete between the presence or absence of S and T antigens in all the strongly oncogenic lines before and after passage *in vivo*. It is noteworthy, however, that in the case of the lines that originally exhibited small numbers of T-positive cells (lines M and 2Ps), all or nearly all of the homologous tumor cells were capable of synthesizing this antigen.

Immunofluorescence tests for the presence of anti-T antibody in the sera of animals bearing large tumors induced by intramuscular implantation of the 6 strongly oncogenic lines are also recorded in the table. As expected, this antibody was detected only in sera from animals bearing tumors in which T antigen was demonstrable.

DISCUSSION

Although the possibility still remains that the emergence of neoantigens following exposure to SV40 depends upon derepression of cellular antigens, much evidence is now at hand favoring the view that T antigen in non-virus-producing SV40-exposed cells depends upon the persistence of viral genetic material. Our findings, that S antigen appeared in cells of hamster embryo lines previously exposed to SV40 but not in cells of the unexposed homologous lines maintained under the same conditions, provides additional data suggesting that this antigen may also depend upon persistence of the SV40 genome.

If it be assumed that information for the synthesis of both antigens is provided by the viral genome, the results reported here suggest that the genome may be expressed in one of two ways, i.e., in coding for the synthesis of both S and T antigens or in coding for that of S antigen only. This reasoning is based on the demonstration that in the descendants of 2 of the lines of cells exposed to SV40, S and T antigens were synthesized, whereas in 2 other lines similarly treated S antigen alone was reproduced. Relevent to the foregoing concept are the recent results of Kluchareva and co-workers (1967) indicating that the synthesis of S antigen precedes the synthesis of T antigen. Parenthetically, we may add here that in addition to those postulated, the viral genome may assume still another state which would code for T antigen only. The present experiments, however, afford no indication of whether this may or may not occur.

We have no knowledge of the nature of the factors which determined whether only S antigen or both S and T antigens will be synthesized. One may speculate, however, that these factors are, in part at least, cell-dependent, since in lines of SV40-exposed hamster lung cells (unpublished observations) only S antigen has been demonstrated, whereas in hamster heart cells maintained under comparable conditions both antigens were found (unpublished observations). Uncloned cell lines originating from the mixed tissues of whole embryos were used in the experiments reported here. The observed variation, therefore, in the reproduction of the two antigens among these various lines might reasonably be attributed to differences in composition of cell population, which may have taken place during the long period of independent cultivation *in vitro*. On this assumption one may further conjecture that in certain of the embryonic lines the populations came to consist entirely of cells which were either completely resistant to infection, or, if infection did indeed occur, coding for these antigens by the viral genome was entirely repressed. In other lines we may suppose that only cells permitting the expression of that portion of the genome specifying the synthesis of S antigen were present, while in those lines in which both antigens were found cells allowing complete expression of the genetic factors for each antigen were represented. That population differences existed in two of the lines at least, is given some support by the observation that in the SV40-exposed lines which exhibited cells with S and T antigens, the proportion of T-positive cells was small when first observed and remained constant on further subculture.

In presenting the foregoing ideas it was assumed that the viral genome remains intact, at least in respect to its capacity to provide information for the synthesis of the two antigens. Alternatively, however, one can visualize structural losses in portions of the viral genome specifying one or both of these antigens which might be brought about by factors present in cells of different origin. If a way can be found to recover infective virions from cells of the lines synthesizing only S antigen, evidence might be obtained in support of one or the other of the mechanisms just proposed. Thus, should structural loss of a portion of the genome be responsible, cells which are potentially capable of synthesizing both antigens should be found to synthesize *only* S antigens when exposed to infective virus recovered from S-positive, T-negative lines. With this possibility in mind, experiments will be undertaken to determine whether by the cell fusion technique which Gerber (1966) has recently applied to induction of SV40 in non-virus-producing lines, the replication of infective virions in S-positive, T-negative lines can be induced.

In hamster cells previously exposed *in vitro* to SV40 a correlation between the presence of T antigen and the capacity to induce tumor formation has been demonstrated (Diamandopoulos and Enders, 1966). In the present experiments the attempt was made to determine whether in S-positive, T-negative cells a similar correlation could be established. As stated at the beginning, in tests for S antigen in several SV40-exposed, T-negative hamster lung cell lines, S antigen was detected in 3 which were shown to be oncogenic, while this antigen was not found in 3 remaining lines which failed to induce tumor formation. Although these findings suggested a correlation between the presence of S antigen and oncogenicity, this could not be affirmed, since comparable SV40-non-exposed lines were not available as controls. Consequently the possibility remained that spontaneous oncogenic transformation might have occurred independently of the capacity to reproduce S antigen. In the present experiments with hamster embryo cell lines such controls were included. The results, nevertheless, again failed to answer the question conclusively, since not only the two S-positive, T-negative SV40-exposed cultures became oncogenic, but during the same period of observation the two homologous unexposed cultures also acquired this property. However, tumors induced by the 2 S-positive lines (M, and 2Ps) that exhibited a small proportion of T-positive cells, consisted preponderantly of T-positive cells. Therefore, the S-positive, T-negative cells originally present in these lines may not have been oncogenic. Further experiments employing cloned lines from these sources that consist of cells with only S antigen may serve to clarify this point.

The demonstration of the acquisition of oncogenicity by cells in cultures, comparable as far as was known in all respects except for exposure to virus should be noted. It reemphasizes the necessity for the inclusion

Near disaster with the Salk vaccine

THE scientific community is breathing easier over an event that, at the time, seemed to be one of the most horrifying medical mistakes in history.

It is now almost certain that a recently-discovered virus, unwittingly put into hundreds of thousands, if not millions, of doses of early Salk vaccine, will not cause cancer in human beings. But for a while the evidence pointed in the other direction.

The virus, which has been the subject of much secret medical concern, is known as simian virus 40 (SV40). When discovered in the kidney tissues of Rhesus monkeys, SV40 was considered a stray organism, one of many latent viruses that lurk about man and animal without doing any damage.

In 1961, came the frightening report that SV40 could cause cancer when injected in newborn hamsters. Alarm gripped every public health man in the country. Hundreds of thousands of children had been infected with this virus since the Salk vaccine was introduced in 1955.

Considerable comfort, however, was taken in the fact that SV40 was dangerous only in newborn hamsters. Furthermore, the dosage needed to infect hamsters was much greater than the children were likely to have gotten.

But the report touched off a flurry of research activity on SV40 and produced more disturbing findings. The tumor-producing property of SV40 was not limited to the hamster, it was discovered. A rat species also came down with tumors.

In August, 1962, a leading investigator found the hamster could be infected as late in life as 22 days, a period that corresponds more closely to the age of younger children who received most of the vaccine. There also was some evidence the SV virus could produce slight, non-cancerous infection in man, and when put in human tissue culture could cause some cell changes suggestive of tumor growth.

This meant a definite study had to be made of the statistics in the Salk-treated children themselves. The National Institutes of Health undertook that analysis.

Fortunately, a tidy, built-in experimental model existed because the early use of Salk vaccine was controlled. In 1954, Salk vaccine was field tested among 400,000 first-, second- and third-grade children in 44 states. In 1955, it was licensed as a commercial product and administered to first and second graders in all states under a free vaccination program by the National Foundation. By July, 1955, six million children had been inoculated.

The stored specimens of the vaccine lots were available in Washington. They were analyzed for simian virus content and matched against the death rates in the various states.

The results, published in *The Journal of the American Medical Association*, were gratifying. They showed the mortality rates in cancer have been no greater in the four years since 1955 than in the four before.

There is a slight increase in leukemia, but the same increase is shown in states receiving no SV40 in the vaccine.

"There is no reason to suspect the slight increase in leukemia mortality rates is related to SV40," said the experts, Dr. Joseph F. Fraumeni, Jr., medical officer, and Dr. Robert W. Miller, chief of the epidemiology branch of the National Cancer Institute.

The comparisons were made only to 1959 because complete vital statistics are only available to that point.

Since the incubative period of a potential cancer virus may be longer than four years, continued surveillance will be necessary.

It would be premature to conclude that SV40 is harmless, Dr. Fraumeni says, but the lack of effect thus far is highly encouraging.

SV40 also has been involved in the early Sabin vaccine. It may be included in further study. Since its discovery, however, SV40 has been rigidly excluded from both Sabin and Salk vaccines.

Comfort can also be drawn from an event in the 1930's when several million people were vaccinated against yellow fever virus.

This virus was propagated on chick embryos. Years later it turned out that chickens harbor one or more viruses that produce cancer in chickens.

These presumably went into the vaccine that treated millions of people, but there is no evidence of an increase in cancer incidence in this group.

—*Arthur J. Snider*

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Edited by **DOUGLAS M. CONSIDINE**

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ETTING EFFECT. The falling-off in brightness toward the gin of an illuminated field, due to the mutilation of the more ique bundles of light by the combined effects of diaphragm and s aperture. This is a source of trouble in photographic objectives en they are used at large apertures, or close to the limit of their ly-illuminated fields.

NCENT'S ANGINA. Ulcer.

NEGAR EEL (*Nematoda*). A minute roundworm, *Anguillula rbatrix*) *aceti*, found in the "mother" of vinegar. It reaches a gth of 2 millimeters. The worms have been found in other situa-s, including the human bladder.

NYL CHLORIDE. Chlorine Organics.

NYON FIBERS. Fibers.

PER FISHES (*Osteichthyes*). Of the order *Isospondyli*, family *adiodontidae*, viper fishes have an unattractive, snake-like appear-e, which is dramatized by their large fanglike teeth. The three cies all inhabit deep ocean waters, ranging from very cold to pical. The longest of these species attains a length of about 10 hes. In catching its prey, the fish swims with its mouth wide open l upper fangs extended so as to spear the victim. Studies have wn that these fishes engage in vertical migrations, moving upward ne 1,500 feet at night, but not known to surface.

PER (*Reptilia, Sauria*). A poisonous snake with a pair of long ular fangs near the front of the upper jaw. Most species of vipers also characterized by the relatively short and thick body and the ad triangular head. The group includes the typical vipers of the l World and the pit vipers of North and South America.

The Old World vipers include a number of Asiatic, European, and ican species bearing the name viper and in addition the two cies known as the asp and eja. The Egyptian horned viper is metimes known as the cerastes from the name of the genus to ch it belongs. The African puff-adder is a viper, named from its of inflating the body when disturbed. This name has unfor-ately been borrowed for an entirely harmless snake of the eastern ited States, related to the hog-nosed snake. It is variously known he puffing or spreading adder or blowing viper. When disturbed it tens its body and makes an impressive bluff, but it is quite nless.

Many of the Old World vipers are dangerous. Their poison is ilar in nature to that of the pit vipers.

RAL PNEUMONIA. Respiratory System.

REO. Warbler.

RGA. Hydrometeors and Precipitation.

RGO. One of the earliest named constellations; the sixth sign of Zodiac. References to Virgo are found in every known literature are always connected in some manner with a maiden and the est. Among the Egyptians, Virgo was associated with Isis, who said to have formed the Milky Way by dropping innumerable at heads in the sky.

stronomically, the constellation is famous for the large cluster of xies found in it. Sir William Herschel found no less than 323 xies in this part of the sky, and more recent observations have ed the number to more than 500. It also contains a large number ariable stars and the well-known bright star, Spica. (See map mpanying entry on Constellations.)

RGO CLUSTER. A cluster of galaxies totaling more than 300 ers and occupying an area approximately 12° in diameter. of the galaxies are spirals, a fact which may be due to the close ximity of this cluster. The distance to the Virgo cluster is approxi-ely seven million light-years. See also Galaxies.

RTUAL OBJECT (Optics). Object (Real).

VIRTUAL TEMPERATURE OF AIR. Atmosphere (Earth).

VIRTUAL WORK. Work (Virtual).

VIRUS. Viruses are considered to be the smallest infectious agents capable of replicating themselves in living cells. The majority of these extremely small infectious particles fall within a size range of about 0.02–0.25 micrometer and can only be visualized directly with the aid of an electron microscope. The precise mechanism of how a virus transfers its nucleic acid to the host cell, and how the normal function of the cell is directed toward the production of progeny, remains obscure. Although extensive research continues, viruses pose some of the most fundamental problems encountered in molecular biology. Until about the early 1960s, viruses were named for the diseases which they caused—thus mumps virus, measles virus, influenza virus, yellow fever virus, smallpox virus, etc. It is only within relatively recent years that large quantities of several of the viruses can be obtained *in vitro* in cell cultures. Better methods of virus purification have enabled investigators to carry out chemical tests which were hitherto impossible. Many of the biological tests for viruses, such as complement fixation, hemagglutination, or cytopathic changes in cell cultures and serum-virus neutralization tests in cell cultures or animals, are extremely sensitive, and these methods are used routinely for viral identification. There are a few viruses, however, whose identification depends upon biochemical tests, and still others for which biochemical tests in conjunction with biological tests are useful aids for identification. Progress has been made in the classification of viruses beyond simply associating them with the names of the diseases which they cause.

Viruses studied in detail have a core of nucleic acid surrounded by a protein coat or coats. The viral nucleic acids are of two types, ribose (RNA) or deoxyribose (DNA). They represent the genetic material necessary for the replication of intact virus progeny. Nucleic acid extracted from purified virus using phenol or dodecyl sulfate is easily destroyed by the homologous nucleases which are present in normal sera or tissues. DNA is destroyed by the enzyme deoxyribonuclease and RNA by ribonuclease, and this is one means of identifying the type of nucleic acid. The intact virus is not affected by these enzymes.

Without a protein coat, the nucleic acid is ordinarily incapable of entering a cell. Entry can be accomplished by washing the cells to remove any serum and by pretreating the warmed cells with hypertonic salt solution. On entry into the cell, the viral nucleic acid induces the synthesis of a new protein coat from the host material. Some viral nucleic acids are capable of replicating at least one virus cycle in hosts which do not permit replication by the whole virus. Poliovirus nucleic acid has been known to give rise to whole virus in embryonic chick cells, a host which is not susceptible to infection with poliovirus; polyoma virus nucleic acid has produced whole virus in *B. subtilis*, a bacterium. In general, the DNA viruses multiply in the nucleus of the host cell and RNA viruses in the cytoplasm. Some of the RNA viruses appear to emerge as buds from the cell membrane as seen in the electron microscope.

The nucleic acids and the proteins which they control exist in an orderly fashion. In the RNA viruses, the nucleic acid may be in either a cubical or a helical form; the DNA viral nucleic acids occur only in a cubical form. The cubical nucleic acids are enclosed in a container or capsid made up of similar protein subunits or capsomers in crystalline array, usually as an icosahedron. Certain groups of viruses are consistent in that they are the same size, and the number and arrangement of the capsomers are the same. In some of the RNA viruses the nucleic acid is arranged as a double- or single-helical structure surrounded by protein subunits. The combination of nucleic acid and protein may constitute the whole virus, or there may be additional outer membranes which contain lipids. Viruses which have lipid membranes can usually be inactivated by ether, chloroform or bile salts.

The two groups of viruses RNA and DNA are further divided according to size, morphology, and biological and chemical properties. Thus the cubical RNA viruses which are ether stable are divided into the picornaviruses and the reoviruses. The name picornavirus comes from "pico" meaning "very small" and "rna" indicating the type of nucleic acid. Included in the group are the enteroviruses: polio, Coxsackie, and foot-and-mouth, etc. The reoviruses cause inapparent infection in humans and other animals, and their relation-

as in producing vaccine-induced en

to spontaneous disease is uncertain. They are morphologically ilar to the wound-tumour virus of clover, and a small cross ctivity with this virus by means of complement fixation has been eported.

The arboviruses are those which undergo a biological cycle in both rthropods and vertebrate hosts. Not all of these viruses have been tudied for fundamental chemical characteristics. Those which have en studied were found to be cubical RNA viruses, sensitive to the ction of ether and relatively unstable.

The myxoviruses and rabies are examples of RNA helical viruses, hich contain an outer, etherlabile, lipid-containing membrane. The yxoviruses include the influenza, parainfluenza, mumps, newcastle, man SV5 and SV11, and possibly also measles, rinderpest and dog stemper viruses. Most of the myxoviruses have an affinity for ucins. They adhere to the surface of erthyrocytes causing them to gglutinate, and the substance responsible for the adhesion is neuraic acid. Adsorption to the cell surface is inhibited by mucoroteins which are present in sera and other biological fluids. *Vibrio olera* produces an enzyme known as receptor destroying enzyme DE), which when added to erythrocytes prior to adding virus, hibits cell attachment and prevents hemagglutination. Less is own about the biochemical aspects of measles, dog distemper, derpest or rabies viruses.

Information is lacking concerning the symmetry of a large number RNA ether-sensitive oncogenic viruses. The fowl leucosis, murine ukemia and mouse mammary carcinoma viruses make up this up.

ll of the known DNA viruses have cubical symmetry. Two groups ich are ether stable are the papovaviruses and the adenoviruses. ere are also two groups of DNA viruses which are generally ether nsitive: the herpes viruses and the pox viruses. All of the herpes uses are ether labile, but ether stability varies within the pox virus up. See also **Recombinant DNA.**

The chemical nature of many viruses, which either do not grow l or do not lend themselves to purification, is unknown. The Riley dehydrogenase virus is a nonpathogenic virus which is gnized only by an increase in lactic dehydrogenase in the blood nfected mice. A lipovirus described by Chang causes marked radation of infected cells and releases a lypogenic toxin dissoe from infectivity, which is capable of inducing fatty degenera- in other uninfected cells. A marked increase in the maglobulin fraction of blood serum of mink infected with Aleumink disease is an indication of infection with a virus which es a color change in the fur and often sickness and death.

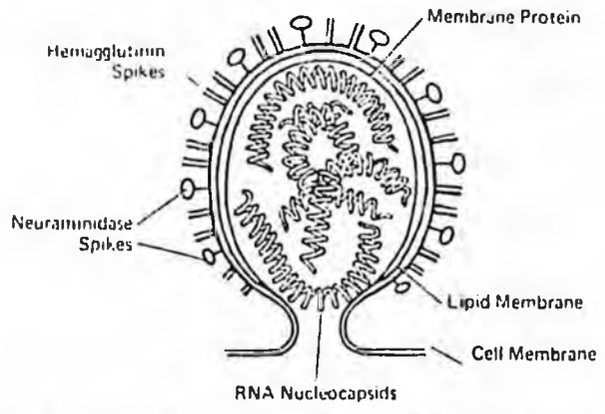
he chemical characteristics of viruses are not only an aid in their dication and identification but are also useful in understanding ature of known viral or viral-induced host antigens and possibly e control of disease. The adenoviruses, for example, contain at three protein moieties, and certain types are capable of inducing or more new host antigens—the chemistry of which is unknown resent. The viral proteins can be separated by gel diffusion and ated with complement fixation. One moiety is the toxic protein h causes the host cell to degenerate; another corresponds to the p antigen common to all the 31 types of adenoviruses; the third type specific protein.

number of viruses induce the host cell to elaborate a substance n as interferon which will inhibit the growth of many viruses in of the same species but not in cells from other animal species. ferons produced by an influenza virus and also a herpes virus both active against the vesicular stomatitis virus. They both d to be proteins of low molecular weight, trypsin sensitive, and at a temperature of 70 C and over a wide range of pH (1–11).

luenza Virus. Many virus diseases, in essence, have been con- d or well controlled without the need really to understand the ate mechanics of the virus. If malaria, for example, can be con- by the eradication of mosquitos, if yellow fever, smallpox, clitis, and measles can be controlled by isolation of the virus the production of vaccines, there does not exist an immediate to solve the problem at the level of molecular biology. However, nted out later, the relationship between what have appeared to ntrollable viruses and later appearance of serious diseases by a *slow virus* series of events, may point to the fact that a person ering from measles, mumps, etc., may have only partially con- d the devastation of the virus and suffer some years later from conditions provoked by an earlier virus infection.

In contrast with the aforementioned common virus diseases, it appears that the solution to the problem of periodic pandemics of influenza may come only from a much better understanding of the virus forms which cause the disease. The persistence of influenza appears to derive from a unique genetic plasticity, allowing the viral agent to undergo at least two kinds of antigenic shift. There is the frequent shift, occurring once about every year or so which appears to stem from minor mutations, thus providing the new variant with an increased resistance to prevailing antibodies. And there is the less frequent (once in 10 to 12 years) antigenic shift that, unfortunately, overcomes all prior immunities. Over 50 million cases of influenza in the United States were reported during the 1968–1969 winter. These cases were attributed to a hitherto unknown variant, first isolated in Hong Kong (hence Hong Kong "flu"). Some 20,000 and possibly as many as 80,000 deaths resulted from this influenza invasion and the side effects which it produced. In the 1972–1973 winter season, a much milder and minor variant, called the London "flu," caused well over 2,000 deaths in the United States, particularly from side effects, mainly pneumonia. When combined with influenza, pneumonia is the fifth most serious public health problem in the United States. In terms of absenteeism, it is the number one problem. In the influenza pandemic of the winter of 1917–1918, over 20 million persons died worldwide, with better than one-half million fatal cases in the United States.

Myxovirus influenzae is the agent of influenza, of which there are three antigenic types, A, B, and C. The first two types occur frequently. Only type A has been found to be capable of producing pandemics. It is presumed that the B virus has a reduced ability to undergo gross antigenic mutations; and that the C virus has no such capability. The influenza A virus is identified as a medium-size RNA virus, some 110 nanometers in diameter and delimited by a membrane. The latter is composed of lipids and polysaccharides derived from the host cell and virus-specific protein. Five distinct proteins have been identified, three of which are inside the virion (part of virus circumscribed by lipid membrane). A schematic diagram of the influenza virus emerging from a cell is given in the accompanying figure.



Schematic representation of an influenza virus emerging from a cell. (*After Kilbourne*)

It has been reported that the antigenic shifts are manifested in hemagglutinin and neuraminidase, two glycoproteins found on the surface of the influenza virion. It is suggested that the hemaglutinin binds the virus to the target cell and when the hemagglutinin function is inhibited (as by an antibody), the virus is no longer effective. It is believed that the neuraminidase cleaves a glycosidic bond in the host cell membrane. This action frees the newly formed virus from the cell. It is believed that this action, if inhibited, will not reduce the infectivity of the virus, but will deter the spread of virus particles to other cells.

The abrupt emergence of new influenza subtypes appears to be too marked to be explained fully by conventional concepts of mutation. It is believed that the explanation rests in the very nature of the viral genome. It has been postulated that if a host cell is infected by two different subtypes of influenza virus at the same time, the genes from the subtypes may undergo a random reassortment in the cell, resulting not only in production of the two original subtypes, but of one or

eral subtypes as well. Each hybrid, of course, will have a different, but full set of genes and recombination within the infected host can explain the large mutations which occur about once every decade. However, it is well established that only one influenza subtype can exist in humans at any given time. Thus, the question of a host in which such recombinations can take place? It has been found, for example, that the emergence of a new subtype, such as the Hong Kong strain, will be accompanied by the abrupt disappearance of the antecedent subtype—thus indicating little if any opportunity for recombinations to occur within human cells. Of considerable interest, however, is the fact that several virus strains can exist simultaneously within various animal hosts. In animals, the appearance of a new influenza virus strain is not necessarily accompanied by the disappearance of previously recognized strains. It has been established that there are at least two discrete subtypes of equine influenza, eight or more avian strains, and a couple subtypes in swine. Thus, the postulation of recombination occurring within animals which share the general environs with humans. Some evidence of this may derive from the fact that most new subtypes appear to originate in Asia, where animals and humans commonly inhabit the same buildings.

Influenza vaccines produced to date are based upon killed viruses. Some authorities believe that attenuated live viruses could be more effective in creating immunity as well as causing fewer undesirable side effects. However, a major problem in connection with influenza vaccines has been the short time allowed for the production of a new vaccine upon the emergence of a new influenza variant. Vaccines made with live viruses have been used in the U.S.S.R. for many years. They have not been licensed in the United States out of fear of over- or underattenuation of the virus. Although the vaccine problems have been largely overcome for other diseases, they have not been solved for the influenza virus because of the almost continual appearance of new variants and the need to continuously change the vaccine formulations.

Among several interesting proposals in recent years, the concept proposed by St. Groth and under study by C. Hannoun and associates at the Pasteur Institute in Paris, is of particular note. This concept, in essence, involves forcing a recent variant of influenza, such as the A_3 subtype, to undergo mutations at an accelerated rate under laboratory conditions until an end point in the evolution of the subtype is reached. It is interesting to note that discovery of the London influenza variant, first isolated in 1972, was antigenically similar to the first mutant that Hannoun and associates had "artificially" produced in the laboratory a year earlier. By gaining a year or more on the natural processes of creating mutants, possibly by way of animal source channels, vaccines could be produced well in advance of the appearance of the mutated virus.

Cytomegalovirus. Surpassing rubella virus, this is the most common viral cause of mental retardation. It has been estimated (late-1975) that cytomegalovirus (CMV) causes serious mental retardation of one of every 1,000 infants, or more than 3,000 infants annually in the United States. Immunosuppressed patients, such as those suffering from cancer, organ transplants, etc., also are prone to infection with CMV. In addition to mental retardation, the disease in infants may cause blindness and deafness. In about 90 percent of the infants, affected by CMV, the disease can be detected only through examination of the urine. In about 10 percent of the cases, the disease is typified by enlargement of the spleen and liver, blood abnormalities, and hepatitis. Microcephaly (abnormally small head) is also sometimes an indication. CMV causes enlargement of the affected cells (cytomegaly). The disease is found throughout the world. Investigators believe that congenital infections are the result of the mother having a primary infection sometime during pregnancy. Investigators believe that CMV, like herpesviruses, persist in a latent stage for long spans of time.

Slow Viruses. During the last decade or two, there has been increasing speculation and some tentative evidence that so-called *slow viruses* may be operative and may be the underlying causes of a number of degenerative diseases, long poorly understood, such as multiple sclerosis and rheumatoid arthritis, among others. More recently, there have been increasing postulations of an association between viruses and diabetes. In fact, rather positive identification of slow viruses with some rare diseases has been established. Most investigators caution that the term "slow" should not necessarily be fully interpreted in terms of a virus per se, but equally if not completely with the manifestations of the virus. So-called slow virus infections are characterized by a long incubation period, followed by a protracted course of disease. The slowness may arise in some cases from the virus itself, but the slow pace also may be the result of weak but prolonged interactions between the virus and the host's immune system. It is also possible that these characterizations of slowness may not be attributable to viruses at all, but to some other unknown causative factors. Obviously as of this juncture, investigators are following a source of suspicion rather than a chain of hard evidence. Nevertheless, the case for the slow viruses is becoming increasingly convincing. The causative agents for at least four rare diseases, two in humans and two in animals, are sometimes referred to as "unconventional viruses."

One of these diseases in humans is *kuru*, encountered only in the Fore people and their neighbors in New Guinea. The disease for many years was considered a genetic disease. However, it has been established that the disease can be transmitted to chimpanzees by injection of extracts from the brains of human kuru victims into the brains of chimpanzees. Kuru is a neurological disease with brain lesions located mainly in the gray matter. The cerebral cortex takes on a spongy appearance. The other human disease is Creutzfeldt-Jakob disease, rare but of worldwide distribution. It involves the premature development of the mental deterioration sometimes seen in old age. It also has been established that it is caused by a transmissible agent that can infect chimpanzees and lower primates. One of the animal diseases referred to is *scrapie*, known for over two centuries as a fatal disease among sheep. The other animal disease is *transmissible mink encephalopathy*, first discovered in Wisconsin in the late 1940s. A puzzling aspect of the unconventional slow viruses is the fact that they cannot be observed with an electron microscope. Another puzzling aspect is their apparent lack of antigenicity. To date, it has not been possible to demonstrate that any of these four "agents" will evoke production of antibodies. These unconventional slow viruses are not destroyed by ultraviolet radiation, and they are highly resistant to treatment with formalin or heat, but infectivity is destroyed by phenol or ether. Some investigators believe that these agents may incorporate a very small nucleus of the size range of the viroids (self-replicating infectious RNA molecules known to produce certain plant diseases).

Two slow infections of the human central nervous system, *progressive multifocal leukoencephalopathy* (PML) and *subacute sclerosing panencephalitis* (SSPE) are thought to be associated with conventional viruses. Although PML does not cause inflammation of the brain, it does produce demyelination, i.e., destruction of the layers of membranes surrounding nerve axons. Some investigators believe that the virus is a papovavirus (group of small viruses including human wart virus, simian virus 40, and the polyoma virus of mice). It is reasoned that in PML the virus destroys the cells needed for formation and maintenance of the myelin sheath. A conventional virus has been isolated from the brains of persons suffering from SSPE. An association between measles (occurring in patients under two years of age) and later development of SSPE (approximately within six years) has been shown by one study.

Slow viruses are becoming increasingly suspect in the instances of much more common diseases, particularly the autoimmune diseases. An autoimmune disease may be defined as a disease wherein the immune system of the body does not direct its attack on an invading foreign substance, but instead at the body's own tissue. Many authorities consider rheumatoid arthritis and multiple sclerosis as autoimmune diseases. The precise causes of these diseases have remained obscure. Multiple sclerosis is a demyelinating disease and has variously been described as an autoimmune disease, a viral disease, or an autoimmune disease provoked by a virus. Epidemiological studies indicate that from 3 to 23 years may elapse between the time of exposure to the virus and the onset of symptoms. Further evidence points to involvement of a myxovirus. Measles virus is of this kind.

Possible Viral Connection to Diabetes. A Norwegian physician (J. Stang) in 1864 noted that diabetes developed in one of his patients within a short period after a mumps infection and was probably the first person to indicate a possible connection between viruses and diabetes. Over the years, numerous other connections have been attempted to relate diabetes with mumps, hepatitis, rubella, coxsackie and influenza viruses, adenoviruses, enteroviruses, and cytomegalovirus. One of the presumptions made is that viruses are understood

to replicate in the pancreas. Commencing in the late 1950s, more substantive evidence has been given. Reports from Sweden in 1958 link juvenile diabetes with mumps infection. Reports from New York State in 1974 relate closely the cycles of incidence of mumps and those of juvenile diabetes. The study was based upon investigation of records for the period 1946–1971. Tentative conclusions indicate an average lag period of about 3.8 years between onset of diabetes and exposure to mumps and it is reasoned that this represents the time required for the virus to produce permanent damage to the pancreas. Other investigators have statistically linked diabetes to rubella (German measles). Some authorities suggest that the pancreas, along with other embryonic organs, may be damaged by the virus that causes congenital rubella. The records of nearly 3,000 juvenile diabetics treated at King's College Hospital in London (1955–1968) have been studied and reveal a seasonal pattern to the onset of juvenile diabetes, striking a low incidence in June and a high incidence in October. Without presenting the details, conclusions are suggested that an association of viral infections with the juvenile form of diabetes is evident. However, the relationship, if any, has not been determined in the case of the maturity-onset form of diabetes.

Phage. Bacteriophages are viruses that invade bacterial cells and are replicated within the bacterial cells. The presence of phage in live virus vaccines has precipitated concern among some authorities. It has been established that phage are introduced into vaccines when viruses for the vaccines are grown in tissue culture. To eliminate these phage, vaccine producers would have to use only sterilely collected serum. This, of course, is difficult and costly. There is far from full agreement that phage-contaminated vaccines are harmful to humans. Some situations, however, have been postulated. Some human diseases, such as scarlet fever and diphtheria are caused indirectly by bacteria, i.e., by bacteria that are infected with phage, the human disease resulting from toxins produced by the bacteria as a result of their virus infection. It is theorized that an individual might take an oral polio virus vaccine that was contaminated with phage that infects corynebacteria and thus cause them to secrete diphtheria toxin. Thus, if the intestinal bacteria included susceptible corynebacteria, that person could contract diphtheria. Another effect of phage is that they can transmit genes to human cells in tissue culture. Phage can carry a specific gene lacking in human cells. If exposed to such phage, the human cells would start to synthesize the protein coded by that gene. It has been suggested that it is in the realm of possibility for phage to transmit genes to human cells and thus cause cancer or degenerative diseases in humans.

A link between viruses and cancer has been debated for a number of years. See also Cancer.

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VIRUS INSECTICIDES. Insect Control and Insecticides.

VISBREAKING. Petroleum.

VISCACHA. Rodentia.

VISCERA. Organs lying more or less freely in the cavities of the body. Usually applied to the heart and lungs as thoracic viscera and to the stomach, intestines, spleen, liver and pancreas, and some of the reproductive organs as abdominal viscera.

VISCERAL ARCH. The column of tissues persisting between adjacent gill slits in the wall of the vertebrate pharynx. The arch is lined with endodermal tissue and covered outside with ectodermal. It contains a bony or cartilaginous support belonging to the visceral skeleton and an aortic arch. In the fishes the gills are supported by these arches. See also Fishes.

VISCERAL MASS. A compact mass of tissue containing some of the internal organs of the mollusks. It forms the main part of the body.

VISCOELASTICITY. Mechanical behavior of material which exhibits viscous and delayed elastic response to stress in addition to instantaneous elasticity. Such properties can be considered to be associated with rate effects—time derivatives of arbitrary order of both stress and strain appearing in the constitutive equation—or hereditary or memory influences which include the history of the stress and strain variation from the undisturbed state.

VISCOSITY. A property of fluids which appears as a dissipative resistance to flow. A solid which is subjected to external forces can attain a condition of elastic equilibrium with elastic stresses balancing the applied forces. A fluid subject to external forces can be in static equilibrium only if the forces are derivable from a potential function and the usual result is steady flow resisted by viscous stresses set up by distortion of fluid elements. The mechanism and nature of the viscous effect may be very different in gases and in liquids.

In a gas, viscous stresses arise from migration of molecules which carry with them momentum relative to their starting-points. To the extent that the gas may be treated as a continuous fluid, i.e., on scales large compared with the mean free path and for time intervals large compared with the collision frequency, Newton's law of fluid friction is obeyed. The elementary form of the law is that, in simple shearing motion, the shear stress is proportional to the rate of shear. More generally, the stress tensor p_{ij} is linearly related to the rate of deformation tensor

$$s_{ij} = \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}$$

the mercury contamination already present in the bottom, but would also prevent any problems associated with sediment migrations. The disadvantages are the cost, the permanence of the plastic seal, and the unknown ancillary ecological effects that would result form the destruction of the benthic ecosystem.

8. **Remove the mercury contamination by amalgamating it with aluminum or other active metals[911]** – This method involves adding aluminum or some other metal which will actively react with mercury to form an amalgam and thereby remove it from the biological methylation cycle. The primary disadvantage of this proposal is that it adds another metal to the aquatic ecosystem, while the unknown parameters of this proposal are its cost and the possible ecological damage from the introduction of the amalgamating metal.

9. **Decontamination of streams and lakes through the use of clams to "biologically mine" the mercury contaminants[961]** – Under this proposal, clams would be used to remove the mercury contamination biologically from an aquatic ecosystem. The great advantage of this method of mercury removal is that it would cause the least ecological damage to the aquatic environment. Among the disadvantages, the possibility exists that mercury contamination might increase because the clams disturb the bottom sediments. Also, the effectiveness of this method must be questioned. For example, assuming that clams could concentrate as much as 20 ppm of mercury in their flesh, the harvesting of each million pounds of clams would result in the removal of only 20 lb of mercury from that aquatic ecosystem. Moreover, once the clams have been harvested, they would represent a costly solid waste disposal problem.

Chapter VIII

EPIDEMIOLOGY AND TOXICOLOGY OF MERCURY

Summary

During the last two centuries an estimated 1,800 to 2,000 individuals have been poisoned by some form of mercury with an estimated 120 to 150 deaths. Among these poisonings, the number attributed to organomercurials is estimated at between 700 and 800 people, including over 125 deaths. Furthermore, the vast majority of the organomercurial poisonings are due to alkylmercurials such as methyl or ethylmercury. The potency of the alkylmercurials as poisons is reflected in the fact that they were responsible for the disasters which occurred at Minamata, Japan (1953 – 1959), Niigata, Japan (1964-1965), Iraq (1956 and 1960), Pakistan (1961), Guatemala (1964-1965), and the U.S. (1969-1970). Alkylmercurials afflicted about 700 individuals and caused about 120 deaths. Therefore, while it is important to recognize that all forms of mercury are powerful poisons, the alkylmercurials are many times more effective poisons than either the inorganic or arylmercurials.

From a toxicological point of view, the pharmacological activity of inorganic and organic forms of mercury differs greatly, not only in the extent to which they are absorbed by the body but also in the degree of injury they inflict on the body. Furthermore, it appears that the distribution of various forms of mercury in animal tissues is a function of the metabolic process of the animal. If all factors were equal, the relative concentrations of inorganic, aryl and alkyltype mercury compounds in the blood, brain, kidney, and liver tissue would be present in the following declining order

alkyl > aryl > inorganic,

while the concentrations of inorganic, aryl, and alkylmercury found in the different organ tissues are present in the following declining order

kidney > liver > blood > brain.

Inorganic forms of mercury taken orally are not absorbed very quickly by the body. And once absorbed, approximately 50% of the mercury is transported by the blood plasma and it is quickly excreted in the urine in this form. Conversely, the organic mercury compounds, especially the alkylmercurials, are more toxic than the other kinds of mercury compounds because the human body absorbs more and excretes less of them. Therefore, larger amounts of the organomercurials are stored in the various tissues of the body. In addition, alkylmercurials, such as methylmercury, easily pass the blood-brain barrier to accumulate in the brain where they destroy selected brain cells and thereby produce the specific symptoms associated with alkylmercurial poisoning. Alkylmercurials also pass easily across the placental barrier causing mercury levels in the fetal red blood cells to be 20 to 30% higher than the mother's red blood cells. It has been established that the developing fetal nerve tissue is very sensitive to the destructive effects of alkylmercurials and congenital neurological damage has been reported in human fetuses at levels that have not produced alkylmercury poisoning symptoms in the mother.

Therefore, it appears that inorganic or arylmercurials pose no real threat to man or the environment directly. However, since almost any form of mercury entering the aquatic environment can be biologically converted to methylmercury, it may ultimately become necessary to control all forms of mercury pollution.

EPIDEMIOLOGY OF MERCURY

While the cumulative poisonous effects of mercury have been known for centuries, it was not until 1557 that Jean Fernel provided the first description of industrial mercury poisoning.[6] By the end of the 16th century, mercurialism associated with the cinnabar mines at Almadén[361] and Idria[362] prompted the Spanish and Austrian governments to grant the miners shorter working hours and longer vacations.

One of the first recorded and a most unusual mass mercury intoxication occurred at Idria, Austria in 1804. As a result of a fire in a local mercury mine,[364] 900 inhabitants who were exposed to mercury vapors in the air developed mercurial tremors. Besides the people, cows and other domestic animals showed similar symptoms. In 1810, another extraordinary wholesale poisoning by metallic mercury vapor occurred on the British sloop *Triumph*. After the vessel salvaged a cargo of mercury from a disabled Spanish ship, the mercury seeped into the hold and bilges of the *Triumph*. The mercury vapors that escaped killed 3 sailors and severely poisoned 200 others.[364]

In the U. S. the first known outbreak of mercurialism occurred in New Jersey in 1860. This incident was traced to the use of carroted fur that contained excessive amounts of mercury.[365] In 1891, Adler[366] gave a clinical description of chronic mercurialism in five human males. Within the felt manufacturing industry, chronic mercury poisoning was highest among blowers and shippers, the two occupational groups that were exposed to the highest concentrations of mercury vapor.[367] Among men employed in the repair of direct current meters, the occurrence of chronic mercury poisoning was described in 1949.[368] Symptoms were found only in men who repaired mercury-containing direct current meters but not in men who tested nonmercury-containing alternating current meters. Furthermore, the incidence of mercury poisoning varied according to the atmospheric concentration of mercury in their respective working environments. Four cases of subacute or chronic mercurial poisoning were found among men who operated high frequency induction furnaces where the power was supplied by an oscillating current, high frequency converter that had a mercury discharge gap.[369,370] Other occupational intoxications occurred when policemen used mercury powder to develop fingerprints.[371-373] These incidents demonstrate that the possibility of mercurial poisoning exists whenever mercury or mercury-containing compounds are used carelessly.[374-385] Lee substantiates this with additional examples of mercury poisoning in his discussion of the history of the statutory control of mercury poisoning in Great Britain.[386]

Isolated cases of organomercurial poisonings most commonly result from the accidental or uninformed misuse of mercury in agricultural products. Since organomercurial compounds were introduced to prevent seed borne diseases in 1914, a number of people have been fatally poisoned or severely incapacitated. Individual poisonings have commonly resulted from eating food products such as bread or porridge made from cereal grains treated with some form of alkylmercury fungicide.[78-84] Another source of mercury poisoning that may well be more prevalent than has been realized previously results from the accidental, inadvertent, or intentional feeding of dressed seed grain to farm livestock. This problem came to public attention in the U.S. in December, 1969, when three members of an Almagordo, New Mexico family were stricken with classical symptoms of alkylmercury poisoning.[78,387,388] An investigation revealed that the head of the family had fed some hogs discarded waste seed grain that had been treated with an organomercurial fungicide. Moreover, the scientific literature contains a disturbing number of cases of livestock poisoning by organomercurials that were severe enough to warrant investigation.[81-83,389-391] But, of course, a number of organomercurial poisonings that were not severe enough for the farmer to call a veterinarian are not recorded.

Kurland et al.[10] have summarized 39 cases of human organomercurial poisoning that have been reported in the literature from 1865 through 1954. Some typical examples of organomercurial poisonings can be considered here. Lundgren and Swensson[392] described 9 cases of alkylmercury poisoning which not only involved ingestion of treated seeds, but also toxic human exposure to alkylmercury-treated lumber and seeds. Taylor et al.[393] established higher urinary and blood mercury levels in 33 employees of an alkylmercury seed-dressing operation. Hill[394] reported that the deaths of 2 female stenographers were caused by

vapors of an alkylmercurial stored in a room adjacent to their office. Ahlmark[395] described 4 cases of alkylmercury poisoning associated with seed-dressing or wood impregnation operations. There are many additional references which deal with the poisonous nature of organomercurials in fungicides.[396-399]

Several accounts of poisonings with phenylmercuric compounds have also been reported. McCord et al.[400] established that phenylmercuric oleate possesses skin irritant properties. Goldwater et al.[401] reported that an individual sprayed with a mixture containing 12% phenylmercuric acetate received second degree chemical burns of his skin, but had an uneventful recovery. In an earlier study, Goldwater and Jeffers[402] described the mercury poisoning of nine workers using a special antifouling marine type paint. With regard to the use of arylmercurials as water-based paint preservatives, various investigators[401,403,404] have established that the [illegible]icological hazards involved with phenylmercuric [illegible]cetate appear to be minimal.

But since antiquity, mercury-containing compounds used in medicines have also caused mercurial poisoning. For example, the use of various organomercurials as diuretics has been associated on many occasions with incidents of toxicity.[405-407] The extent of the pathological changes that are induced appears to depend both on the type of mercurial used and the duration of the administration, but it is not necessarily related to the drug's efficacy as a diuretic. Thus, Mercaptomerin sodium (Thiomerin®) virtually lacks the cardiac toxicity which is common to other organomercurial diuretics.[408-411] But in high doses it is lethal and induces cortical renal necrosis without the apparent glomerular involvement that is typical of mercurial damage.[412] Several mercury preparations for diuresis in cardiac edema patients have been associated with incidents of poisoning. The toxicosis is manifested in various ways from mild cases to death. Some of the proprietary mercurial diuretics are Salyrgan®, Merbaphen®, Mercupurin®, and Esidrone®. All poisonings that have resulted from their use reflect variations in individual susceptibility to a particular mercurial. Merbaphen was the first deadly mercurial diuretic to be identified with three fatalities.[413] And Salyrgan was reported to cause death after it was administered intravenously.[414-416] Neptal®[364] and Mercupurin[417-420] have also been associated with fatalities. However, probably some of the deaths were not due to the direct toxic effects of the mercurials. Therefore, the part played by the mercurial diuretics in these cases cannot be determined directly. However, some deaths must be attributed to the drug itself.

In general, the toxic manifestations of mercurial diuretics can be grouped into three classes:

1. Symptoms related to and resulting from the associated diuresis which are essentially nonspecific.
2. Direct toxic effect of the mercury ion on spec[illegible] organs. Within this class, renal lesions consist of degeneration of the proximal tubular epithelium and cause albuminuria. In immediate fatality cases following intravenous administration of mercurial diuretics, death is the result of a direct action of the mercury ion on cardiac musculature.[421-424] The effect is manifested early as a change in intraventricular conduction and later as terminal ventricular fibrillation.
3. Generalized manifestations of an idiosyncrasy or an allergic reaction which include such reactions as chills, fever, dermatosis, or leukopenia.[425-433]

Until the early 1950's, recognized [illegible] mercury poisoning usually involved individuals who were associated with industrial or occupational exposure to mercury intoxication. For example, as late as 1954, only 39 cases of organomercurial poisoning had been reported in the literature.[10] Most of these cases resulted from exposure to the organomercurials during the processing or use of seed disinfectants and a few cases resulted from laboratory exposure. B[illegible] in 1953, a mysterious new type of neurological disease afflicted the inhabitants of Minamata, Japan.[11,16,434-441] After years of investigation, in 1959 the causative agent was conclusively proven to be methylmercury. The methylmercury was a by-product when mercuric sulfate and chloride were used to convert acetylene into acetaldehyde and vinyl chloride. The highly poisonous methylmercury was discharged into Minamata Bay as part of the wastewater effluent from a plastics factory. And the methylmercury subsequently accumulated in the fish and shellfish in Minamata Bay. Between 1953 and 1961, 121 cases including 46 deaths by methylmercury

poisoning were officially reported. The disease primarily afflicted fishermen and their families. Over 1% of a population of 10,000 people living in the vicinity of the Bay suffered some effect from the disease. Today the term "Minamata Disease" is used to describe the chemical and pathological characteristics of this neurological disorder. And the term "Minamata Disease" has become synonomous with methylmercury poisoning specifically and alkylmercury poisoning in general. In 1965, a similar epidemic again resulted from the discharge of methylmercury in the wastewater effluent from a chemical company into the Agano River near Nugata, Japan. This epidemic caused 47 more cases of Minamata Disease and 7 deaths.[388, 439-443] In addition, Ui and Kitamura[444] reported preliminary findings which indicate that a serious mercury pollution problem also exists in Italy. As at Minamata and Nugata, Japan, a factory in Ravenna, Italy produces acetaldehyde from acetylene with a mercury catalyst, and the wastewater effluent is discharged into a nearby lagoon. Fish taken from the lagoon near the wastewater effluent discharge point show a mercury accumulation of from 1 to 2 ppm on a wet weight basis.

Human mercury intoxication has not occurred in the local Italian population because the fish are not used for food. The fish are not consumed because they have a strong chemical smell and taste as a result of the heavy pollution in the lagoon. However, seagulls that feed on these fish have accumulated a high mercury content in their feathers. The authors of this report also established that the total mercury content of the feathers is 17 ppm, with 91% methylmercury. This value is about the same as that found by Johnels and Westermark[389] in Swedish seabirds of prey such as the Osprey (*Pandion haliaetus*) and the Great Crested Grebe (*Podiceps cristatus*), both of which are near extinction.

Whereas the Minamata and Niigata epidemics resulted when methylmercury was released into the environment as a by-product from a chemical manufacturing process, other alkylmercury poisoning epidemics were directly associated with the agricultural uses of alkylmercury-containing fungicides. Several alkylmercury poisoning epidemics have been recorded. In the Guatamalan Highlands, 45 cases of organomercurial poisoning resulted in 20 deaths in 1965.[60] In Pakistan, about 100 people were similarly afflicted in 1961.[64] The exact number of cases is difficult to determine because undetermined numbers of people were afflicted with mild symptoms in nearby villages, and the cause of their affliction was not identified and the numbers were not recorded. Also, some people died at home, while others were admitted to local hospitals or were treated as out patients. Nevertheless, of the 34 patients who were hospitalized, 4 died, and 5 seriously ill patients were removed by relatives. Their subsequent fate was not recorded. Among the remaining 25 patients, 14 had mild cases, 7 were moderately severe, and 4 were severe.

In northern Iraq in 1956 more than 100 cases of mercury poisoning and 14 deaths were diagnosed.[63,446-447] In 1960, many farmers were poisoned and 221 patients were admitted to one hospital in Baghdad, Iraq. Other patients were known to have been stricken by ethylmercuric chloride. Furthermore, scientific reports in the Russian literature identify organomercurial poisoning incidents in that country also.[62,448-449]

TOXICOLOGY OF MERCURY

As with most substances, the toxicological effects and pharmacological activity of mercury are determined by the form and quantity in which the mercury compounds are administered.[401-404] However, as with any toxic substance, the dose alone determines the poisonous nature of that substance.

Hughes[403] has shown that both the biological effect and the variation in distribution are principally due to the reaction with thiols to form mercuric mercaptides and the natural distribution of thiols in the tissues determines the degree of reaction and accumulation. This partially explains the affinity of mercury for human plasma which is rich in the thiol groupings. However, the organomercurials, especially methylmercury, have a relatively high solubility in fat although this varies with the size of the organic molecule. And these organomercurials diffuse easily through cell membranes, thus, they account for the uniform distribution throughout the body. In addition, physiological and cytological studies have established that methylmercury tends to be associated with red blood cells and the nervous system. Furthermore, methylmercury easily passes the blood-brain and placental barriers to accumulate in the brain and fetus.[405] In contrast, the inorganic salts of mercury show a strong affinity for a large number of groupings on proteins. This causes them to crowd onto a few molecules, and distribution is delayed among the available thiols throughout the body. Consequently, extreme local irritation is produced.[403]

Inorganic mercurial salts, on the other hand, characteristically show low blood levels, but with a predilation for the kidney, liver, and spleen. Evidence indicates, therefore, that pathological effects of mercury intoxication correlate very closely with the real concentration of the metal in the affected organ as well as with the sensitivity of the organ to mercury.[406] It also is evident that mercury has threshold values for the different organs which must be exceeded for the symptoms of intoxication to be observed.[407,408]

In order to assess the potential hazard of mercury and its compounds on man and the environment, it is important to distinguish among the various forms of mercury compounds. Basically, all mercury compounds can be categorized as either inorganic or organic. The inorganic mercury classification includes mercury in the form of (1) the elemental liquid metal and its vapor, (2) the mercuric ion (Hg^{++}) and its salts, (3) the mercurous ion (Hg^{+}) and its salts, and (4) mercuric ion complexes which are capable of forming reversible bonds with the thiol groups in proteins. The organomercurial classification includes chemical compounds which contain carbon atoms that are covalently bound to a mercury atom. The organomercurial compounds can be further categorized into subclassifications according to the organic functional group attached to the mercury atom. In the consideration of the toxicological effects of mercury compounds, the most important of these subclassifications are the aryl, alkyl, and alkoxyalkyl. Their generalized structures are

arylmercurial alkylmercurial alkoxyalkyl mercurial

where R is any alkyl group such as methyl, ethyl, propyl, etc.

The differentiation among these subclassifications of organomercurial compounds and their toxicological properties is primarily a function of the combined physical and pharmacological or clinical properties of each category. These toxicological differences are most important because alkylmercurial compounds show a great propensity to accumulate in nervous tissue. Therefore, they have a far greater neurotoxicity than aryl or inorganic mercury compounds.

The toxic manifestations of mercury may be acute or chronic; and, in general, industrial poisoning tends to be chronic, while nonindustrial poisoning is acute.

ACUTE MERCURY INTOXICATION[401,409-410]

The acute symptoms that result from ingestion or injection of any mercury-containing compound include: burning in the mouth and throat; eschar on the mouth and lips; extreme salivation and thirst; nausea; vomiting of blood-stained mucus; severe gastrointestinal irritation, severe abdominal pain; shock; bloody diarrhea; loss of fluids and electrolytes; rapid weak pulse; cardiac arrhythmias; cold, clammy skin; pallor; slow breathing, and peripheral vascular collapse. After from one day to two weeks, the following delayed actions occur: ulcerative colitis; salivary gland swelling; excessive salivation; metallic taste; stomatitis; foul breath; loose teeth; soft, spongy gums; and a blue-black gum line caused by mercury-sulfhydryl complex may become evident.

Oliguria is often present with anuria, uremia, albuminuria, hematuria, proteinuria, and acidosis. Death at this stage is ascribed to uremia. Autopsies reveal inflammation and extensive corrosion along the alimentary tract, severe renal tubular necrosis, and, possibly, central necrosis of the liver.

The acute symptoms that occur when inorganic mercury compounds are inhaled include stomatitis, salivation, metallic taste, abdominal cramps, diarrhea, difficulty in breathing, cough, restlessness, fever, rapid respiration, gastrointestinal and central nervous manifestation, bronchial irritation, pneumonitis, and kidney damage with renal shutdown.

CHRONIC MERCURY INTOXICATION[401,409-410]

The manifestations of chronic mercury intoxication are most commonly encountered in industry, among dentists and their patients with

mercury amalgam fillings, and in laboratory research workers. These manifestations result from prolonged exposure to excessive concentrations of mercury vapor or the dust of mercury salts.

With chronic mercury poisoning all of these symptoms may appear, but usually the onset of these symptoms is slow and insidious. While the symptoms are extremely variable, they are known to include:

1. *Central nervous system* – Headache, vertigo, vasomotor disturbance, ataxia, peripheral neuritis, muscular tremors, and pain and numbness in the extremities.

2. *Gastrointestinal* – Increased salivation, stomatitis, gingivitis with blue line, loss of appetite, weight loss, nausea, vomiting, diarrhea, swollen salivary glands, soft spongy gums, metallic taste, foul breath, and occasional liver damage.

3. *Genitourinary* – Proteinuria, hematuria, anuria, and nephritis with renal damage progressing to acute renal failure with anuria.

4. *Respiratory* – Inflammation of the nose (rhinitis), loss of smell (anosmia), cough, and fever.

5. *Skin* – Erythematous papular, vesicular lesions and urticaria progressing to weeping dermatitis.

6. *Eye* – Constrictions of the visual fields and mercurialentis which is due to the deposition of mercury on the anterior and posterior surfaces of the lens.

7. *Muscular* – Overall general muscular weakness and fatigue.

8. *Erethism* – A peculiar form of psychic disturbance that results from chronic mercury intoxication. Erethism is characterized by abnormal irritability or responsiveness to stimulation. The symptoms include irritability, stammering, blushing; shyness; anxiety; restlessness; resentment of criticism; insomnia; loss of self-confidence; fear of losing one's job, loss of concentration; loss of memory; loss of drive, energy, or interest; forgetfulness; melancholia; hallucinations; evidence of mental deterioration; mental depressions; and excessive perspiration.

Chronologically, chronic mercurialism usually begins with a progressive numbness of the distal parts of the extremities and often of the lips and tongue. This is followed by an ataxic gait, clumsiness of the hands, dysarthria, dysphagia, deafness, and blurring of vision. This blurring is associated with constriction of the visual fields. Voluntary movements are limited in most patients although muscle atrophy is rarely apparent. Spasticity and rigidity are often present; muscle stretch reflexes are usually preserved or become hyperactive, and extensor plantar responses are occasionally elicited during the later stages. Insomnia, agitation, hypomania, and the loss of emotional control are frequently noted. Stupor and coma predominate in some patients. Most patients have abnormal involuntary movements including choreoathetosis, myoclonus, and coarse resting and action tremors.[10]

The manifestations of chronic mercury poisoning in the central nervous system are associated with certain pathological features that are confined to this system.[illegible] These manifestations include a varying degree of cerebral edema, atrophy of the calcarine, pre- and postcentral cerebral cortex, cerebellar atrophy, and scattered punctate hemorrhages.

Histopathologically, there is a diffuse cellular degeneration with gliosis. The degeneration of nerve cells is not severe in the calcarine and precentral cortex in which the glial proliferations and extensive vacuolization are most prominent. Involvement of the rest of the central nervous system is minimal.[illegible] Similar histopathology of the central nervous system has been described in swine,[illegible] cats, crows, sea birds, and fish that spontaneously succumbed to Minamata disease,[illegible] as well as in experimental animals.[illegible]

In their findings on mice that were experimentally exposed to labeled mercuric chloride, Berlin and Ullberg[illegible] inferred that the localization of mercury at relatively high concentrations in focal areas of the brain correlated well with the areas of pathological lesion development. This appears to confirm an earlier report that mercury concentration corresponds with calcification and atrophy of the granular layer of the cerebellum in rats after their chronic exposure to mercuric chloride.[illegible]

ORGANOMERCURIAL INTOXICATION

While the complete syndrome of mercury intoxication can be induced by either organic or inorganic mercurials, there are some differences in the respective symptoms. Inorganic mercury

poisoning victims have symptoms of stomatitis. Also, excessive salivation and erethism are usually quite pronounced while organic mercury poisoning victims usually experience more severe manifestations of the motor and sensory nerve damage symptoms. In cases of severe alkylmercurial intoxication these symptoms are not reversible, indicating that permanent brain damage has occurred. In addition, because alkylmercurials can pass the placental barrier, congenital neurological injuries can be induced in the fetus. Furthermore, even after acute exposure to toxic concentrations of methyl and other alkylmercurials, it may take weeks or months for the characteristic clinical symptoms to appear.

ALKYLMERCURY POISONING[illegible]

In the case of methyl or ethylmercury poisoning, the acute and chronic poisoning symptoms are quite similar. In an approximate order of mild to severe intoxication they include: excessive fatigue; headache, general overall feeling of weakness, inability to concentrate; amnesia, numbness and tingling of mouth, tongue, lips, hands, fingers, feet, and toes, and ataxia including general clumsiness, impairment of speech, unsteadiness of gait, loss of coordination, and reflex changes. In more severe cases there is a concentric narrowing of the visual field ultimately leading to tunnel vision, loss of ability to speak; impairment of hearing, severe emotional disturbances characterized by unpredictable violent outbursts of anger or fits of depression, and progressive and sometimes complete loss of muscular control, i.e., paralysis and finally death. Moreover, methylmercury salts have been shown to produce toxicity in man when they were applied to the skin in an ointment.[illegible] The lungs and the digestive tract are the most important routes of absorption, however. And the available evidence indicates that more than 90% of the methylmercury in food is absorbed.[484]

ALKOXYALKYL AND ARYLMERCURY POISONING

The organomercurials, methoxyethylmercury and phenylmercury, appear to be quickly metabolized by biological systems into inorganic mercury, which is then eliminated. Therefore, toxicity and chronic symptoms are similar to those associated with mercuric salts, i.e., diarrhea, loss of appetite, weight loss, and fatigue. Relatively few cases of methoxyethylmercury[illegible] or phenylmercury poisoning[illegible] have been reported, and very few cases were seriously intoxicated.[illegible]

ABSORPTION OF MERCURY COMPOUNDS

Mercury and its compounds have an affinity for the thiol groups found in biological protein and enzyme systems. However, the exact compositions of the complexes formed with sulfhydryl-containing substances in the body are not known. Since organic mercurials are strongly complexed by these enzyme systems, the organic mercury salts are more completely absorbed than inorganic mercury salts.

Clarkson[illegible] reported that only about 2% of orally administered inorganic mercury compounds are absorbed. These data appear to conflict with the findings of Fitzhugh et al.[illegible] that rats are capable of absorbing about 50% of the mercuric acetate fed to them.

Organomercurials can be absorbed by [illegible] respiratory tract, and gastrointestinal [illegible] thermore, the hazard of inhalation intoxi[illegible] is increased whenever the organomercurials are highly volatile. Biological systems absorb methyl and phenylmercury compounds unchanged and in much greater quantities than the inorganic mercurials. Fitzhugh et al.[illegible] reported that rats had an intestinal absorption of phenylmercuric acetate of between 50 and 80% of the administered dose. In man, the intestinal absorption of alkylmercurials has been estimated at 90 to 95% of the administered dose.[illegible]

The absorption of inorganic or organic mercury vapor through the lungs poses a special intoxication problem. After exposure to mercury vapor, mercury accumulates in the brain in quantities far in excess of what is found after an equivalent amount of inorganic mercury is administered orally or intravenously.[illegible] In vitro experiments have established that whole blood is capable of absorbing mercury vapor and rapidly oxidizing the metal into the more toxic mercuric mercury. In any case, the brain absorbs less than 2% of the injected dose of mercury. However, when mercury

ermary excretion of about 3.3% in 49 days increased with time for 30 days after absorption.

Therefore, the considerable risk to man from methylmercury (alkylmercurials) must be a result of two parameters. First, the alkylmercurials are much more biologically stable than other forms of mercury compounds. Thus, they resist degradation to inorganic mercury which can be eliminated from the body. The 70-day biological half-life demonstrates this parameter. Second, only the alkylmercurials appear to be able to cross the blood-brain barrier and attack the central nervous system.

The information now available about human

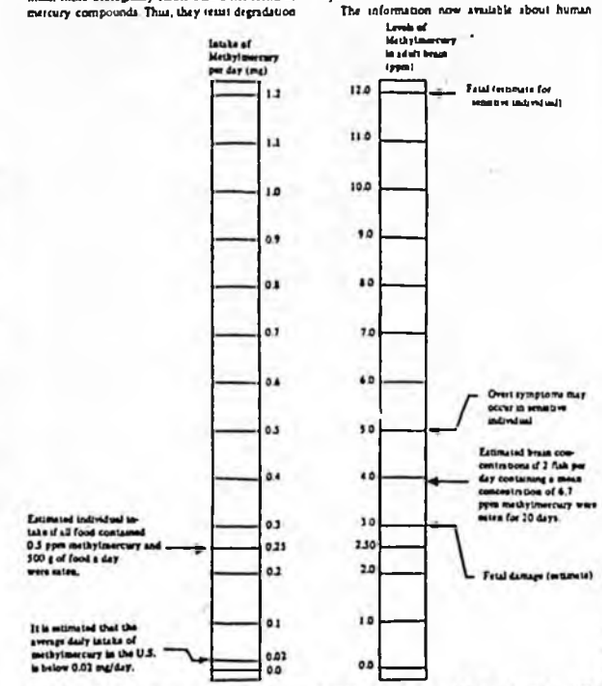

FIGURE 7. Calculated relationship between methylmercury intake and levels of methyl mercury in brain tissue[116] Calculations of brain tissue levels based on: 1. Brain distribution of 15% of total body methylmercury. It has been calculated at 10 to 15%. 2. Continuous exposure for 1 year. With an excretion rate of 1% per day of total body mercury the indicated level will almost be reached. (From Grant, N., *Environment*, 13, 14, 1971, with permission.)

beings exposed to methylmercury is summarized in Figures 7 and 8.[116]

CONGENITAL (OR FETAL) MINAMATA DISEASE

By 1960, it was evident that many children born between 1955 and 1959 in Minamata, Japan suffered from mental retardation and motoric disturbances. This new disease was puzzling initially because the clinical symptoms varied so widely from the adult cases of Minamata Disease that it was difficult to classify them. In addition, none of the afflicted children had consumed any contaminated fish or shellfish; and usually their mothers showed none of the symptoms of Minamata Disease.[119]

The clinical symptoms of children born to mothers who were exposed to alkylmercurial intoxication during their pregnancies were . . . [illegible] to symptoms experienced with severe cerebral palsy or cerebral dysfunction syndrome. These symptoms included a list of disturbances of mind, coordination, speech, and hearing, as well as constriction of the visual field, impairment of chewing and swallowing, enhanced tendon reflex, pathological reflexes, involuntary movement, primitive reflexes, superficial sensation, salivation, and forced laughing.[119] The severity of the disease ranged from children who had mild to moderate ataxia and spasticity to children with all of the listed symptoms. To date, 23 cases of Minamata Disease have been diagnosed, but only 1 of the mothers showed any outward symptoms of Minamata Disease.

The evidence that alkylmercurials cross the placental barrier and produce fetal damage is quite strong. Those infants who died were found to contain high levels of mercury in their kidneys, brain, and liver.[119] Also, Takeuchi established

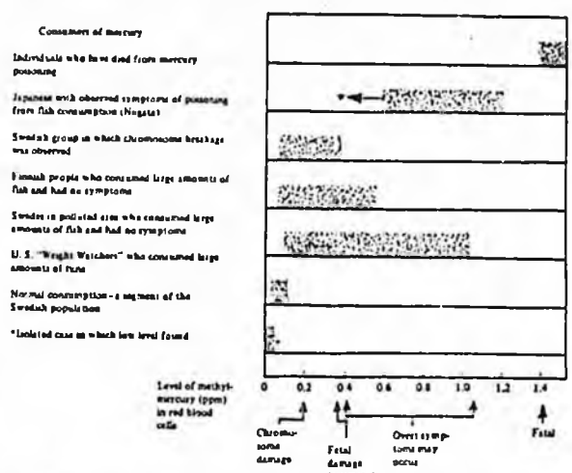

FIGURE 8. Relation of methylmercury levels in blood to physical hazard[116] (From Grant, N., *Environment*, 13, 12, 1971, with permission.)

vapor is inhaled and absorbed, because of its lipid solubility and lack of charge, more than 10% of the dissolved elemental mercury diffuses across cell membranes into the brain tissues.[488-493]

MERCURY DISTRIBUTION IN BLOOD

Inorganic mercury is absorbed into the plasma proteins in the blood. Therefore, it is more amenable to excretion from the body in the urine.[493,494] Alkyl and arylmercurials, on the other hand, are largely bound to the red blood cells, i.e., erythrocytes.[495,501] While mercury levels in the blood as a result of arylmercurials are evenly distributed between the plasma and the red blood cells, the alkylmercurials have a much greater affinity for red blood cells. Berglund and Berlin[441] reported that 90% of the methylmercury present in the blood of all species of animals studied was bound to the red blood cells. These authors also noted that the fraction of methylmercury in plasma varies according to the species as follows: 10% in man and rabbits, 4.5% in rats, and 9% in the squirrel monkey. Moreover, the alkylmercurials differ greatly from other mercurials in their ability to penetrate the blood brain and placental barriers to attack the central nervous system and the fetus. Thus, Berlin and Ullberg[486] reported that 15 to 20% of the total mercury in the body can be found in the brain.

No useful correlation factor has been found between the intake and concentration of mercury in the urine or blood after exposure to elemental or inorganic mercury compounds. However, since methylmercurials are slowly eliminated from the body, mercury levels in the blood can be used as an index of exposure to these compounds. For example, Tejning[497-510] reported that "normal mercury levels" in a 21 year-old man who never ate fish were 4.6 ppb in the blood cells. Among 58 men and 25 women in Sweden who ate fish at least once a week, the average mercury levels of the red blood cells were 9.87 ppb and 10.48 ppb, respectively. Blood plasma levels were also higher than Tejning's "normal" at 2.01 and 2.83, respectively. Sumari et al.[511] and Burke et al.[512] also confirmed that the mercury levels in the red blood cells and plasma provide at least a qualitative diagnostic index for methylmercury intoxication.

METABOLISM AND TISSUE DISTRIBUTION OF MERCURY COMPOUNDS

The two most important differences between the aryl- and alkylmercury salts are the rate at which each is eliminated from the body and their ability to penetrate the blood-brain and placental barriers to attack the brain and the fetus. Of most importance is how quickly the organic mercury compound can be metabolized into inorganic mercury which is more readily excreted from the body. Arylmercurials are rapidly metabolized by the body, whereas the more metabolically stable alkylmercurials resist degradation into inorganic mercury. Clarkson[513] theorized that perhaps the reason the alkylmercurials give no symptoms until after a latency period of one to two weeks is related to the slow rate of metabolic cleavage of these compounds. Therefore, the greater toxicity of the organomercurials, especially the alkylmercurials, could be explained largely by their greater absorption with less excretion and consequent storage in the organism.

Metabolism and tissue distribution of the various mercurials have been studied by means of radioactive tracers. With this method, a correlation has been established between the species of animal tested, the administered mercury dose, the mercury body burden, and the toxic effects of selected inorganic and organic mercurials. Moreover, it has also been established that not only are organomercurials not metabolized in the same manner as inorganic mercury compounds, but it appears that the distribution of aryl and alkylmercurials in various animals is related to their differences in metabolism. Furthermore, the rate at which organomercurials are metabolically degraded varies among different species of animals.

Differences in the metabolism of aryl and alkylmercurials have been demonstrated in various investigations of animals. For example, after a single dose of phenylmercuric acetate has been administered intravenously, intramuscularly, or orally, it is rapidly metabolized to inorganic mercury.[389,514-518] And the distribution of the metabolized phenylmercuric acetate in each organism is very similar to that produced by inorganic mercury with the highest levels found in the liver and kidneys and usually no detectable levels in the brain. In contrast, Swensson et al.[515] found that a single intramuscular injection of methylmercury dicyandiamide was uniformly distributed throughout the tissues of the body, and only a very little was detected in the brain. Later, the same authors[519] established that when this alkylmercurial was repeatedly administered, it caused an appreciable accumulation of mercury in the brain.

Investigating the distribution, metabolism, and excretion of phenylmercuric acetate and methylmercury, Gage[520] found that phenylmercuric acetate is unchanged when it is absorbed into the circulatory system. The phenylmercuric acetate is metabolized by the liver and kidneys and excreted in the feces and urine, mostly as inorganic mercury. No measurable amounts of mercury were found in the central nervous system. Furthermore, in cases where phenylmercuric acetate is continually administered, a steady condition is reached after approximately 14 days. Then the excretion of mercury nearly balances the intake. However, methylmercury accumulates in all tissues, particularly in the red blood cells. Repeated doses of methylmercury produce no clear indication that a steady state can be reached after 6 weeks. Rather, the mercury levels in the brain increase progressively. Inorganic mercury is slowly released from tissues, particularly in the intestines and muscles. Overall, however, methylmercury is much more slowly released from the tissues than phenylmercuric acetate, and the subsequent metabolism of methylmercury into inorganic mercury is low. The major route of excretion is in the feces.

Miller et al.[516] administered phenylmercuric acetate intravenously, intramuscularly, and orally to chicks, rats, and dogs. They found that the compound is absorbed unchanged with less than 10% of the initial dose excreted unmetabolized in the urine. The unchanged phenylmercuric acetate is transported by the blood into the circulatory system where it is converted into inorganic mercury through metabolism in the liver and kidneys. Then it is excreted in the feces and urine. Metabolism in the biological systems that were tested is rapid. For example, phenylmercuric acetate is detectable in the animal for only 96 hr after it is administered. In another study, Miller et al.[521] administered ethylmercuric chloride intramuscularly and orally to chicks and rats. Once again, the compound was absorbed unchanged by the organism, but in contrast to phenylmercuric acetate, ethylmercury is detectable in the livers and kidneys for at least 21 days. In addition, it was established that ethylmercury was present to a greater extent in the chick's liver than in its kidney, whereas in the rat the alkylmercurial was found predominantly in the blood and kidney. Also, while the excretion of mercury in the rat's urine was not as rapid as for phenylmercuric acetate, the mercury levels in the rat's kidneys showed a marked increase that indicated a slow metabolic conversion of ethylmercury to inorganic mercury. Furthermore, the fecal excretion of ethylmercury was minimal, and only 5% of the amount observed in the phenylmercuric acetate study was eliminated during the 7 days after its initial admission.

Ellis and Fang[522] studied the elimination, tissue accumulation, and cellular incorporation of mercury in rats that received oral doses of mercuric and phenylmercuric acetate. They showed that the highest concentrations of mercury were in the kidneys, followed by the liver, lung, and heart in declining order. The major route of excretion for both classes of mercurials was via the feces with only small amounts excreted in the urine. The average total excretion in one week reached 98 and 80% of the administered doses of mercuric acetate and phenylmercuric acetate, respectively. These elimination values show that 68 and 80% of a single dose of phenylmercuric acetate were excreted in the feces and urine while in the same period 35% of the inorganic mercury was excreted in the feces and between 1 and 4% in the urine. The similarity in these excretion patterns was related to the rapid metabolic conversion of phenylmercuric acetate to inorganic mercury.

METABOLISM, DISTRIBUTION, AND EXCRETION OF METHYLMERCURY IN MAN

In order to elucidate the mechanisms of methylmercury metabolism in man, radioactive methylmercury was administered orally to three male volunteers.[523-528] Within 15 min, their red blood cells absorbed the compound, and the mercury accumulated in the patients' livers and heads. The livers and heads accumulated about 50 and 10%, respectively, of the body burden of the methylmercury nitrate. The biological half-life for methylmercury in man was found to be between 70 and 74 days. The main excretory route was the feces with about 33% in 49 days. However, the

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AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

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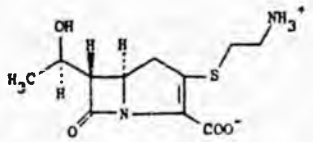
al., Ibid. **15**, 518 (1979). Prepn of *N*-formidimidoyl thienamycin: W. J. Leanza *et al., J. Med. Chem.* **22**, 1435 (1979); T. W. Miller, Eur. pat. Appl. 6639 (1980 to Merck & Co.). *C.A.* **93**, 155845y (1980); B. G. Christensen *et al.*, U.S. pat. 4,194,047 (1980 to Merck & Co.). Evaluation of *in vitro* and *in vivo* activities: H. Kropp *et al., Antimicrob. Ag. Chemother* **17**, 993 (1980). Comparative study vs gram-positive and gram-negative aerobic and anaerobic species and β-lactamase stability: H. C. Neu, P. Labthavikul, *ibid.* **21**, 180 (1982). Pharmacokinetics, bacteriological efficacy: P. Patamasucon, G. H. McCracken, *ibid.* 390.

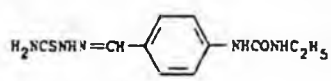


White hygroscopic solid. $[\alpha]_D^{25}$ +82.7° (c = 1.0 in water). uv max (water, pH 4-8): 296.5 nm (ε 7900). (pH 2): 309 nm; (pH 12): 300.5 nm. Freely sol in water, sparingly sol in methanol. In dilute soln, stability is optimal between pH 6-7, declining with unusual rapidity above that range. Susceptible to inactivation by dilute solns of hydroxylamine and cysteine.

N-Formamidoylthienamycin monohydrate, $C_{12}H_{17}N_3O_4S \cdot H_2O$, *6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino]ethyl]-thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate, thienamycin formamidine monohydrate, MK-0787, MK 787, imipenem, imipemide.* Cryst from water-ethanol. $[\alpha]_D^{25}$ +86.8 (c = 0.05 in 0.1 *M* phosphate, pH 7). uv max (water): 299 nm (ε 9670, 98% NH_2OH ext).

THERAP CAT: Antibacterial.

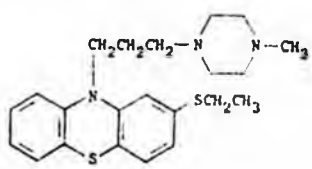
9150. Thiethazone. *2-[[4-[[(Ethylamino)carbonyl]amino]phenyl]methylene]hydrazinecarbothioamide; 1-ethyl-3-(p-formylphenyl)urea thiosemicarbazone;* ethylurcidobenzaldehyde thiosemicarbazone; thioethazone. Tebacyl. $C_{11}H_{14}N_4OS$; mol wt 265.35. C 49.79%, H 5.70%, N 26.40%, O 6.03%, S 12.09%. Prepd from ethyl thiocyanate + 4-aminobenzaldehyde thiosemicarbazone: Brit. pat. 672,370 (1952 to A. Wander).



Fine yellowish crystals, mp 220° (decompn).

THERAP CAT: Antitubercular.

9151. Thiethylperazine. *2-(Ethylthio)-10-[3-(4-methyl-1-piperazinyl)propyl]phenothiazine;* 3-ethylmercapto-10-(1'-methylpiperazinyl-4'-propyl)phenothiazine. $C_{22}H_{29}N_3S_2$; mol wt 399.62. C 66.12%, H 7.31%, N 10.51%, S 16.05%. Prepn: Bourquin *et al., Helv. Chim. Acta* **41**, 1072 (1958).



Crystals from acetone, mp 62-64° bp$_{0.01}$ 227°.

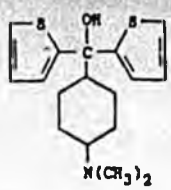
Dimaleate, $C_{30}H_{37}N_3O_8S_2$. *Forecan Maleate, Toresten, Trestén.* Crystals from methanol, dec 188-190°.

Dihydrochloride, $C_{22}H_{29}N_3S_2 \cdot 2HCl$, crystals from ethanol, mp 214-216°.

Dimalate, $C_{22}H_{29}N_3S_2 \cdot 2C_4H_6O_5$, crystals from ethanol, mp 139°.

THERAP CAT: Antiemetic.

9152. Thihexinol. *α-[4-(Diethylamino)cyclohexyl]-α-2-thienyl-2-thiophenemethanol; (4-dimethylaminocyclohexyl)-di-2-thienylmethanol; α,α'-*dithienyl-4-dimethylaminocyclohexyl carbinol; Entoquel. $C_{17}H_{23}NOS_2$; mol wt 321.51. C 63.51%, H 7.21%, N 4.36%, O 4.98%, S 19.95%. Prepn: Villani, U.S. pat. 2,764,519 (1956 to Schering).

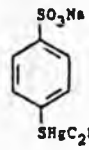


Crystals from benzene, mp 156-157°.

Methyl bromide, $C_{18}H_{26}BrNOS_2$, crystals from ethanol + ether, mp 231-232°.

THERAP CAT: Methyl bromide as anticholinergic.

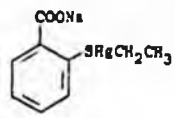
9153. Thimerfonate Sodium. *Ethyl(4-mercaptobenzenesulfonato-S⁴)mercury sodium salt;* sodium *p*-ethylmercurithiophenylsulfonate; ethyl[(*p*-sulfophenyl)thio]mercury sodium salt; Sulfo-Merthiolate. $C_8H_9HgNaO_3S_2$; mol wt 448.88. C 21.79%, H 2.06%, Hg 45.50%, Na 5.21%, O 10.89%, S 14.55%. Prepn: Waldo, *J. Am. Chem. Soc.* **53**, 992 (1931); Kharasch, U.S. pat. 1,672,615.



Powder, very sol in water. Forms a stable solution.

THERAP CAT: Topical anti-infective.

9154. Thimerosal. *Ethyl(2-mercaptobenzoato-S)mercury sodium salt; [(o-carboxyphenyl)thio]ethylmercury sodium salt;* sodium ethylmercurithiosalicylate; thiomersalate, mercurothiolate; Merthiolate; Merzonin; Mertorgan; Merlamin. $C_9H_9HgNaO_2S$, mol wt 404.84. C 26.70%, H 2.24%, Hg 49.55%, Na 5.68%, O 7.90%, S 7.92%. Prepd by reacting ethylmercuric chloride (or ethylmercuric hydroxide) with thiosalicylic acid: Kharasch, U.S. pat. 1,672,615 (1928); Trikojus, *Nature* **158**, 472 (1946); Swirska *et al., Przemysl Chem.* **39**, 371 (1960). *C.A.* **55**, 3507a (1961).

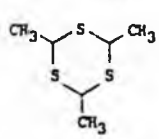


Cream-colored, cryst powder. Stable in air, but not in sunlight. One gram dissolves in about 1 ml water, in about 8 ml alcohol. Practically insol in ether and benzene. Stabilization of solns with EDTA: Davisson, U.S. pat. 2,864,838 (1958 to Lilly). pH of 1% aq soln: 6.7. LD_{50} s.c. in rats 85 mg/kg. Mason *et al., Clin. Toxicol.* **4**, 185 (1971).

THERAP CAT: Topical anti-infective; pharmaceutic aid (preservative).

THERAP CAT (VET): Antibacterial, antifungal—topical.

9155. Thioacetaldehyde. *2,4,6-Trimethyl-s-trithiane;* thioacetaldehyde. $C_6H_{12}S_3$; mol wt 180.35. C 39.95%, H 6.71%, S 53.34%. Occurs in α- and β-forms. Prepn: Baumann, Fromm, *Ber.* **22**, 2600 (1889); Fromm, Engler, *Ibid.* **58**, 1916 (1925). Molecular structure: Hassel, Viervoll, *Acta Chem. Scand.* **1**, 164 (1947). Stereochemistry: Schaberg, Barakat, *J. Chem. Soc.* 1947, 693.



α-Form, monoclinic plates, mp 101°.

...04%, H 10.41%, ...

...0.870. bp 110-11... ...ol in water; miscible with ...

...ls and essences.

Isothiocyanatoethane; ethyl ... 7.15. C 41.34%, H 5.78%, ... Obtained by the action of ... of the reaction of carbon ...

...ngent odor. d_4^{18} 1.003. bp ... 2° Insol in water; miscible ...

Caution: Vapors irritate ...

Methylbutanoic acid ethyl ... ... C 64.58%, H 10.84%, O ... I_3 ... d_{20}^{20} 0.868. bp 135°. ... 1 350 parts water; miscible ...

confectionery and beverages ...

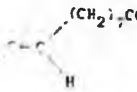
Caryopropanoic acid ethyl ... $C_5H_{10}O_3$; mol wt 118.13. C ... $H_3CHOHCOOC_2H_5$ ... odor. d_4^{14} 1.042. bp 154°, ... 117°F (47°C). Miscible ...), alcohol, ether. *Keep* ...

...lose and cellulose acetate ...

...noic acid ethyl ester. C ... H 12.36%, O 14.0... ...69°, bp_{25} 163°, n_D 1.4321 ... ether.

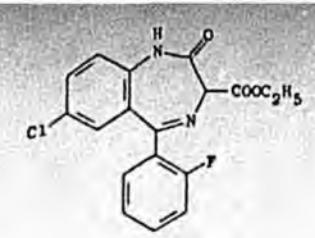
...opentanoic acid ethyl ... ...31%, H 8.39%, O 33.29%. ... n_D^{20} 1.4229. Freely sol in ...

Octadecadienoic acid ethyl ... wt 308.49%. C 77.84% ... from sunflower seed oil ... III, 526 (1955); *see* also ... (1955).



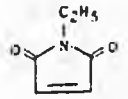
...oxidation than linoleate ... 193°, bp_{25} 175°; bp_{mm} ... value 162.5. Miscible ... oils.

...chloro-5-(2-fluorophenyl)-...azepine-3-carboxylic acid ...orophenyl)-2,3-dihydro-...carboxylate; CM-6912. ... 360.77. C 59.93%, H ... O 13.30%. Benzodia... ...pin. J. Hellerbach *et al.*, U.S. pat. 3,657,223 (1972). Analysis in plasma and ... *Biomed. Mass Spectrom.* ...tabolites: J. P. Cano. *J.* ...cologic evaluation: *G... ol. Ther. Toxicol.* 19, 453 ...



...from ether, mp 193-194°. ... CAT: Tranquilizer (minor).

3767. *N*-Ethylmaleimide. *1-Ethyl-1H-pyrrole-2,5-dione.* $C_6H_7NO_2$; mol wt 125.12. C 57.59%, H 5.64%, N 11.20%, O ... mp 45°. Prepd by heating *N*-ethylmaleamic acid in paraffin ... *J. Chem. Soc.* 1949, 1515.



Crystals, mp 45°. Lacrimator when liquid. ... In cancer research (possible antimitotic activity.) ... Strong irritant.

3768. Ethyl Malonate. *Propanedioic acid diethyl ester;* ...ethyl malonate; malonic ester. $C_7H_{12}O_4$; mol wt 160.17. C ... H 7.55%, O 39.96%. $C_2H_5OOCCH_2COOC_2H_5$. ... Prepd from chloroacetic acid and sodium cyanide followed ... esterification with ethanol and H_2SO_4: L. Gattermann, ... Berlin. *Praxis des Organischen Chemikers* (de Gruyter, ... 40th ed., 1961) pp 220-221.

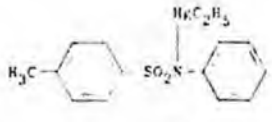
Liquid. Slightly aromatic, pleasant odor. d 1.055. bp ... bp_{12} 95°. mp −50°. n_D^{20} 1.4143. One gram dissolves in about 50 ml of water. Miscible with alcohol, ether ... Manuf of barbiturates.

3769. Ethylmercuric Chloride. *Chloroethylmercury;* ... C_2H_5ClHg; mol wt 265.13. C 9.06%, H 1.90%, ... Cl 13.37%, Hg 75.66%. CH_3CH_2HgCl. Prepd from ethylmercuric bromide by treating with methanolic KOH, filtering and neutralizing with HCl: Slotta, Jacobi, *J. Prakt. Chem.* [2] 120, 249 (1929). Prepn from $HgCl_2$ and tetraethyl ... Whelen, *Advances in Chemistry Series* 23, entitled ... *Organic Compounds* (ACS, Washington, D.C., 1960) ... 12-30. For the prepn of the bromide from ethylmagnesium bromide and mercuric bromide *see* Slotta, Jacobi, *loc. cit.* Marvel *et al.*, *J. Am. Chem. Soc.* 47, 3009 (1925). *Review:* Krause, von Grosse, *Die Chemie der Metall-organischen Verbindungen* (Berlin, 1937).

White silvery leaflets from ethanol, mp 192°. Sublimes ... Solubility in water at 18° = 1.4 × 10⁻⁴ g/100 ml; at ... = 2.5 × 10⁻⁴ g/100 ml; in ethanol at 18° = 0.75 g; at 78° = 3.5 g/100 g; in chloroform at 18° = 2.6 g; ... g. Slightly sol in ether.

USE: Applied at 2% strength (soln or mixed with solids) as a fungicide for treating seeds. *Caution:* Highly toxic ... causes skin burns; is absorbed through the skin. Chronic exposure has caused permanent injury to brain. *Note:* A ... analog *chloro(2-methoxyethyl)mercury, Ceresan Wet*, ... also used as seed fungicide.

3770. *N*-(Ethylmercuri)-*p*-toluenesulfonanilide. *Ethyl-...methyl-N-phenylbenzenesulfonamidato-N)mercury; ethyl-...phenyl-p-toluenesulfonamido)mercury;* Ceresan M. $C_{15}H_{17}HgNO_2S$; mol wt 475.99. C 37.85%, H 3.60%, Hg ... N 2.94%, O 6.72%, S 6.74%.



Crystals. Pungent odor, somewhat reminiscent of garlic. ... insol in water. LD_{50} orally in rats 100 mg/kg. ... Substances List.* H. E. Christensen, Ed. (1973) p 585.

USE: To control the various smuts which befall grain. Reduces bulb rot in gladiolus. *Caution:* Almost as toxic as mercuric chloride *(q.v.)*; less irritating to the skin than ethyl mercury phosphate. Symptoms confined to CNS and consist of deafness, ataxia, dysarthria, progressive visual deterioration; dysphagia; sphincteric incontinence, mental confusion, stupor, death: Gleason *et al.*, *Clinical Toxicology of Commercial Products* (Williams & Wilkins, Baltimore, 3rd ed., 1969) p 68, sect. II.

3771. Ethyl Methanesulfonate. *Methanesulfonic acid ethyl ester;* ethyl methanesulfonic acid; ethyl mesylate; EMS; NSC 26805. $C_3H_8O_3S$; mol wt 124.15. C 29.02%, H 6.49%, O 38.66%, S 25.82%. $CH_3SO_2OCH_2CH_3$. Prepn: O. C. Billeter, *Ber.* 38, 2015 (1905). Mutagenicity studies: T. Alderson, *Nature* 207, 164 (1965); J. B. Jenkins, *Mutat. Res.* 4, 90 (1967); A. P. Schalet, *ibid.* 49, 313 (1978). Review of carcinogenicity studies: *IARC Monographs* 7, 245-252 (1974). Review of comparative mutagenicity of EMS and methyl methanesulfonate, *q.v.*: S. Kondo, *Environ. Sci. Res.* 24, 743-785 (1981).

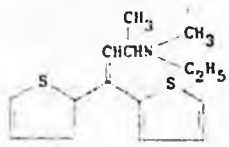
Liquid. bp_{761} 213-213.5°; bp_{10} 85-86°. d_4^{22} 1.1452.

USE: Exptlly as mutagen.

3772. Ethyl Methyl Ether. *Methoxyethane;* methyl ethyl ether. C_3H_8O; mol wt 60.09. C 59.96%, H 13.42%, O 26.62%. $C_2H_5OCH_3$.

Liquid. d_0^0 0.725. bp 10.8°. Sol in water; miscible with alcohol, ether.

3773. Ethylmethylthiambutene. *N-Ethyl-N,1-dimethyl-3,3-di-2-thienyl-2-propenamine; N*-ethyl-*N*,1-dimethyl-3,3-di-2-thienylallylamine; 3-ethylmethylamino-1,1-di(2'-thienyl)but-1-ene; ethylmethiambutene; 1C50; N1H-5145; Emethibutin. $C_{15}H_{19}NS_2$; mol wt 277.46. C 64.94%, H 6.91%, N 5.05%, S 23.11%. Prepn: Adamson, U.S. pat. 2,561,899 (1951 to Burroughs Wellcome). Toxicology: N. B. Eddy, D. Leimbach, *J. Pharmacol. Exp. Ther.* 107, 385 (1953).



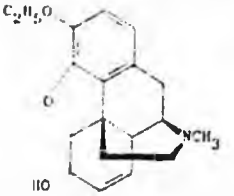
$bp_{0.01}$ 110-113°. bp_{10} 75-76°.

Hydrochloride, $C_{15}H_{19}NS_2 \cdot HCl$, crystals, mp 137-138°. LD_{50} in mice: 192 mg/kg orally; 88 mg/kg s.c., N. B. Eddy, D. Leimbach, *loc. cit.*

Caution: Abuse leads to habituation or addiction.

THERAP CAT: Narcotic analgesic.

3774. Ethylmorphine. *7,8-Didehydro-4,5-epoxy-3-ethoxy-17-methylmorphinan-6-ol.* $C_{19}H_{23}NO_3$; mol wt 313.38. C 72.82%, H 7.40%, N 4.47%, O 15.32%. Prepd by ethylation of morphine: Baizer, Ellner, *J. Am. Pharm. Assoc.* 39, 581 (1950); Gorecki, *Ann. Pharm. (Poznan)* 7, 21 (1969).



Crystals from ethanol, mp 199-201°.

Hydrochloride dihydrate, $C_{19}H_{24}ClNO_3 \cdot 2H_2O$, *Codethyline, Dionin.* White to faintly yellow cryst powder, mp about 123° (dec); anhydrous form, mp about 170° (dec). One gram dissolves in 10 ml water and in 25 ml alcohol; slightly sol in chloroform, ether. LD s.c. in mice 200 mg/kg. *RTECS* Vol. II, R. J. Lewis, R. L. Tatken, Eds. (1979) p 98.

Methiodide, $C_{20}H_{26}INO_3$, *ethyl-N-methylmorphinium iodide, Trachyl.*

Caution: Abuse leads to habituation or addiction.

Life Gets Better

A 1986 survey by The Gallup Poll indicates that only 31 percent of Americans now say they smoke—the smallest percentage of the adult population since the survey began in 1944. At that time, 41 percent of the American population smoked. Smoking reached a high in 1954, when 45 percent of the population smoked. The rate of smoking has been steadily declining since the late sixties.

A recent study of the Nielsen ratings made by the National Coalition on Television Violence (NCTV) shows that the popularity of primetime TV violence is at its lowest point in 20 years. This year only one action program is in the TV top 20.

NCTV believes that this trend is a result of increased public awareness of TV violence and the resurgence of the nonviolent situation comedy.

A Larger View of Abduction

What are the *real* numbers behind the "missing children" statistics? In 1984, the FBI listed 350,000 cases of missing children. Of these, it turns out that 67 were actually kidnapped by strangers. The remaining children were either abducted by parents or relatives engaged in custody battles or else were runaways.

The American Academy of Pediatrics now cautions that fingerprinting and other child identification programs are of limited value and tend to create unhealthy and unnecessary anxiety. Parents may be transmitting fears of stranger abduction to their children, and are advised to consider the "whole story" of the missing children statistics and the possibility of suppressing the child's developing social skills. (*Pediatrics*, 78: 369)

In addition, the "excessive and frightening" use of photographs of missing children on milk cartons, posters, and shopping bags has been under question by a congressional panel. Misleading statistics, bureaucratic infighting, and increasing numbers of businesses hoping to profit from parental fears are under scrutiny. "Public awareness has become public hysteria," says the executive director of a group called Services for the Missing. (*Houston Chronicle*, sect. 1, p. 3, 5 Aug 1986)

Vaccine Update

Confusion surrounds the vaccination question, and the debate continues. Some illnesses that we routinely vaccinate against are virtually nonexistent in this country. Diphtheria is apparently absent from the United States, with no cases reported in 1986. Only three cases had been reported in the two years previous to that. Reported tetanus cases totaled 61 in 1986, and only two cases of paralytic poliomyelitis were reported in 1986.

Pertussis, however, despite near universal vaccination, was more prevalent in 1986 than in any year since 1970. The 1986 total number of pertussis cases was approximately 4,500, with nearly a third of them—1,300 cases—reported in a major outbreak in Kansas. (All 1986 statistics cited above are from the provisional data compiled by the Centers for Disease Control and reported in *Vaccine Bulletin*, Feb 1987, pp. 11-12.)

This outbreak of pertussis in Kansas occurred in a highly immunized population: "Some 90 percent of the pertussis patients whose immunization status was known, appear to have been adequately immunized." (*Vaccine Bulletin*, Feb 1987, p. 11) The outbreak affected all age groups—from 0 to 79 years—with most cases concentrated in those under 20 years

of age. More cases than would usually be expected occurred in the five to nine age group, and less than would be expected occurred among infants.

Vaccine complications continue to receive national press coverage. Some attention has been given to the development of a different type of vaccination for pertussis, one that is associated with fewer vaccine-related complications. The pertussis vaccine currently in use in this country is a *whole-cell* vaccine, which contains dead pertussis toxin—that remains biologically active after the bacteria that secrete it have been killed—as well as endotoxin, a protein secreted by a virus or bacteria that can, in large enough quantities, affect the brain or produce shock. Developed several years ago in Japan, the *acellular* pertussis vaccine has all of the bacteria and most of the toxins removed or rendered harmless, and is considered more pure and specific. Although the acellular vaccine must undergo testing in this country and physicians will not have legal access to it for two to three years, some physicians who are concerned about side effects from the whole-cell preparation are using test batches of the new vaccine for their own children or are traveling to Japan or Hong Kong to have their children vaccinated. (*The New Mexican*, 5 April 1987)

Two preliminary studies of the acellular vaccine in the United States show promising results. Vanderbilt University School of Medicine and the UCLA School of Medicine have thus far conducted studies on 80 children from 18 to 24 months and from

 Illustrations: Ashisha

four to six years of age. Both age groups showed antibody production comparable to the old vaccine, but far fewer adverse reactions in terms of fever, fretfulness, abnormal gait, and redness, tenderness, and swelling at the vaccination site. (*Healthfacts*, vol. XI, no. 90, Nov 1986)

Among the non-Communist countries, only the United States, Australia, and Iceland have mandatory pertussis vaccination programs. And yet, the pertussis inoculation is the most toxic of all protective vaccines routinely given to children in their first five years of life. Each year, this vaccine is linked to the deaths of at least 44, and possibly as many as 900, otherwise healthy children. It also causes more lasting brain damage than whooping cough would if children were not immunized. Most of the whooping cough in America now occurs in vaccinated children or in those too young to immunize. (*The New Mexican*, 5 April 1987)

Both Sweden and Japan experienced an increase in cases of whooping cough after discontinuing mass whole-cell vaccination programs. Japan, now using the acellular vaccine and waiting until two years of age to begin vaccination, has witnessed a dramatic decline in both minor and severe reactions to the vaccine and in cases of whooping cough in general. (*The People's Medical Journal*, Dec 1986)

Many questions remain to be answered regarding the relationship between vaccinations and the decline of an illness in the general population over time; the effect of vaccinations on the immune system; and the safety of administering particular vaccines in a country in which diseases from the conditions vaccinated against are on the decline and in which large numbers of vaccinated people still contract the disease.

Meningitis Vaccine Update

In issue #39, we printed a letter from a reader inquiring about the Hib vaccine, licensed in the United States in April 1985 to protect against the leading bacterial cause of meningitis. Since then, more research has shed light on the problem and on the vaccine. Two recent studies have concluded that *Hemophilus influenza* type b does not seem to spread from child to child as readily as doctors suspected. (*New England Journal of Medicine*) Earlier studies indicated that the infant brothers or sisters of a child with meningitis are up to 400 times more likely to contract this illness; however, one of the more recent studies showed that only one child out of 587 who had regular contact with an infected toddler went on to develop the illness.

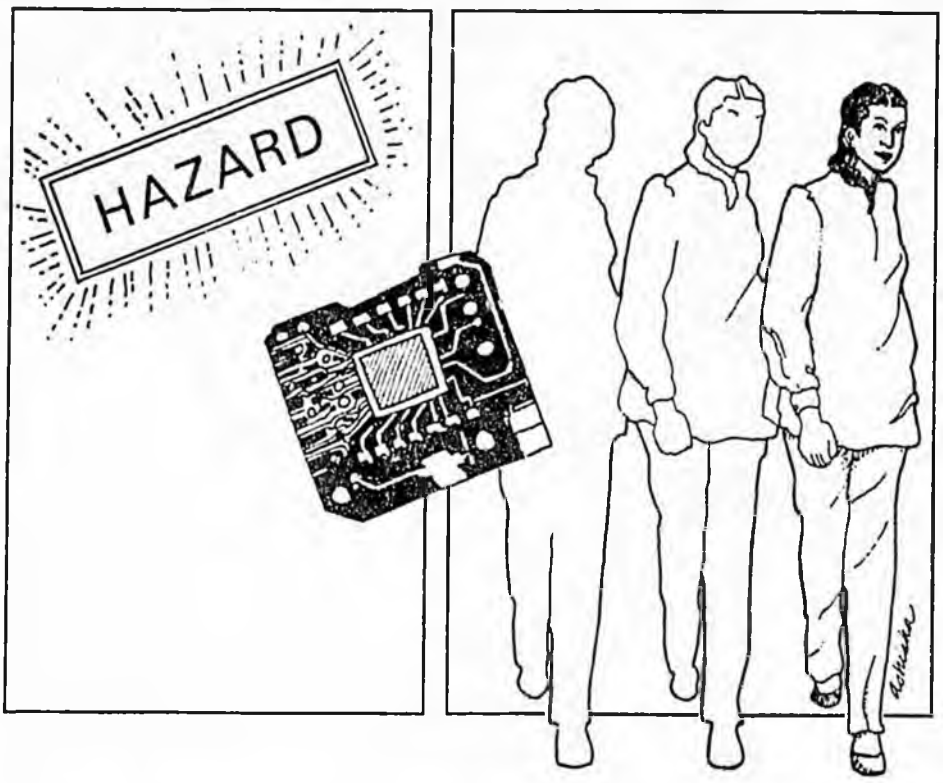
Vaccine failure is also being investigated. Work is under way to determine why it is that some children who receive the preparation go on to develop meningitis. (*New England Journal of Medicine 315*, 18 Dec 1986)

All we can conclude at this point is that contact with meningitis is less "risky" than was formerly believed; that the other causes of meningitis (such as pneumococcus, meningococcus, some viruses, and other agents) are not inoculated against in the current vaccine; that the Hib vaccine is not effective in the under-two age group, in which 75 percent of all meningitis cases occur; and that the current vaccine will not protect all children who receive it.

When the Chips Are Down

Several microelectronics firms are now offering their pregnant employees the opportunity to transfer out of production areas where they may be exposed to chemicals and gases. AT&T has taken this one step further: as of January 1987, they no longer *allow* pregnant women to work on semiconductor production lines.

This concern in the computer manufacturing industry was sparked by a University of Massachusetts at Amherst study conducted since 1984—but not yet formally published—on employees at Digital Equipment Corporation's Massachusetts plant. Results show that women in the micro-



chip etching area had nearly twice the miscarriage rate (39 percent in the first trimester) found in the general population (10 to 20 percent). (*Science News*, vol. 131, no. 5, 31 Jan 1987)

Although the researchers insist that the Digital study does not prove a causal relationship between chip production and miscarriage, and although they are calling for "more extensive exposure measurements," the industry's sensitive response to the data accumulated is to be commended.

CENTERS FOR DISEASE CONTROL

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

January 10, 1986 / Vol. 35 / No. 1

Current Trends

Measles — United States, First 26 Weeks, 1985

Through December 28, 2,704 measles cases in the United States were reported to the *MMWR* for 1985. Results of detailed analyses are available for cases reported during the first 26 weeks, when a provisional total of 1,802 cases was reported, a 2.4% increase over the 1,759 cases reported during the same period in 1984 (1). The overall incidence rate in both years was 0.8 cases per 100,000 population for the 26-week period. Eight states accounted for 1,333 (73.9%) cases: Illinois (259 cases), Texas (236), Arizona (194), California (143), Montana (139), Idaho (126), New York (124), and Massachusetts (112). Ten states had incidence rates greater than 1/100,000 population: Arizona, Hawaii, Idaho, Illinois, Maryland, Massachusetts, Montana, Texas, West Virginia, and Wisconsin. During the first half of 1984 and 1985, 19 and 20 states, respectively, reported measles cases (indigenous or imported). For each year, 2.5% of the nation's 3,139 counties reported measles cases during the period.

Detailed information was provided to the Division of Immunization, Center for Prevention Services, CDC, on 1,801 of the cases reported during the first 26 weeks of 1985. Of these, 1,750 (97.2%) met the standard case definition for measles,* and 661 (36.7%) were serologically confirmed. In most cases (72%), onset of rash occurred between weeks 8 and 20 (weeks ending February 23 and May 25, respectively). There was a biphasic distribution of cases during this period (figure 1).

In the first half of 1984, the highest incidence rate was reported among children 10-14 years of age (Table 1). By comparison, in the first half of 1985, the highest incidence rate was reported among 15- to 19-year-olds (3.1/100,000), followed by preschool-aged children (2.5/100,000). The incidence rate among 10- to 14-year-olds decreased from 2.9/100,000 in 1984 to 1.8/100,000 in 1985. Of the 466 preschool-aged children with measles, 137 (29.4%) were infants under 1 year of age; 81 (17.4%) were 12-14 months of age; 24 (5.2%) were 15 months of age; and 224 (48.1%) were 16 months-4 years of age.

Of the 1,256 (69.7%) patients for whom the setting of transmission was reported, 903 (71.9%) acquired measles in school†, 126 (10.0%), at home, 63 (5.0%), in medical settings; 41 (3.3%), in daycare centers, 18 (1.4%), in church, and 105 (8.4%), in a variety of other settings, including sporting events and summer camp.

Seventy cases (3.9%) were international importations. An additional 128 (7.1%) cases

*Fever (38.3°C [101.9°F] or higher if measured), generalized rash of 3 days' or longer duration, and at least one of the following: cough, coryza (conjunctivitis).

†Includes kindergarten through college.

Measles — Continued

were epidemiologically linked to an international importation within two generations of infection. Therefore, 198 (11.0% of all cases) were classified as international importations during this period (2).

Vaccination status of patients in 1984 and 1985 was similar. Of the 1,801 cases reported during the first 26 weeks of 1985, 859 of the patients had been vaccinated on or after the first birthday; 247 had been vaccinated at 12-14 months of age (Table 2). A total of 846 measles patients were unvaccinated, and 96 had histories of inadequate vaccination (vaccinated before the first birthday).

FIGURE 1. Reported measles cases, by week of rash onset — United States, first 26 weeks, 1985

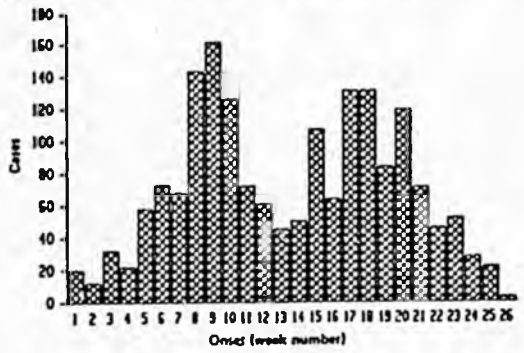


TABLE 1. Age distribution and estimated incidence rates of measles — United States, first 26 weeks, 1984 and 1985*

Age group (yrs.)	1984 No.	1984 (%)	1984 Rate†	1985 No.	1985 (%)	1985 Rate†	Rate change (%)
0-4	351	(19.9)	2.0	466	(25.9)	2.5	+25.0
5-9	201	(11.4)	1.3	152	(8.4)	0.9	-30.8
10-14	515	(29.2)	2.9	315	(17.7)	1.8	-37.9
15-19	470	(26.6)	2.4	603	(33.5)	3.1	+29.2
20-24	137	(7.8)	0.6	175	(9.7)	0.8	+33.3
≥ 25	91	(5.1)	0.1	88	(4.8)	0.1	0.0
Total	1,765§	(100.0)	0.8	1,901	(100.0)	0.8	0.0

*Provisional data.
†Per 100,000 population.
§The difference between this number and that in the text reflects differences between summary data reported to *MMWR* and more detailed data available to CDC's Division of Immunization.

Measles — Continued

Of the 1,801 cases, 466 (25.9%) were classified as preventable (2) (Table 3). The highest proportion of preventable cases occurred among persons who were not of school age: 69.2% of cases among children 18 months-4 years of age were preventable. Only 20.4% of cases among persons 5-19 years of age were preventable; however, 47.0% of all preventable cases occurred in this age group.

Of the 1,335 persons with nonpreventable cases, 242 (18.1%) were too young for routine vaccination (under 18 months of age), and 42 (3.1%) were too old (born before 1957) (Table 4). Of the 1,051 who were between 18 months and 28 years of age, 842 (80.1%) had been vaccinated on or after the first birthday, 11 (1.0%) had a prior physician diagnosis of measles; 34 (3.2%) were not U.S. citizens; and 163 (15.5%) had medical contraindications or exemptions under state law. One person (0.1%) had laboratory evidence of immunity.

Reported by Div of Immunization, Center for Prevention Svcs, CDC.

Editorial Note: In the prevaccine era, an average of 500,000 measles cases was reported

TABLE 2. Ages of measles patients at most recent vaccination — United States, first 26 weeks, 1984 and 1985*

Age at vaccination	1984 No.	1984 (%)	1985 No.	1985 (%)
< 12 mos.	135	(7.6)	96	(5.3)
12-14 mos.	255	(14.4)	247	(13.7)
15 mos.	34	(1.9)	46	(2.6)
16 mos.-4 yrs.	303	(17.2)	335	(18.6)
5-9 yrs.	139	(7.9)	165	(9.2)
10-14 yrs.	32	(1.8)	70	(3.9)
15-19 yrs.	8	(0.5)	5	(0.3)
≥ 20 yrs.	2	(0.1)	1	(0.1)
Unknown (> 12 mos.)	3	(0.2)	8	(0.4)
Unvaccinated	854	(48.4)	848	(47.0)
Total	1,765	(100.0)	1,901	(100.0)

*Provisional data.

TABLE 3. Age distribution and preventability of measles cases — United States, first 26 weeks, 1985*

Age group	Preventable No.	Preventable (%)	Nonpreventable No.	Nonpreventable (%)	Total
< 15 mos.	0	(0.0)	242	(100.0)	242
16 mo.-4 yrs.	155	(69.2)	69	(30.8)	224
5-9 yrs.	32	(21.1)	120	(78.9)	152
10-14 yrs.	52	(16.3)	267	(83.7)	319
15-19 yrs.	135	(22.4)	468	(77.6)	603
20-24 yrs.	60	(34.3)	115	(65.7)	175
25-29 yrs.	32	(60.4)	21	(39.6)	53
≥ 30 yrs.	0	(0.0)	33	(100.0)	33
Total	466	(25.9)	1,335	(74.1)	1,901

*Provisional data.

Measles — Continued

each year (3). After measles vaccine was licensed in 1963, the incidence of measles markedly declined. Since 1981, the number of reported measles cases has remained relatively consistent: 3,124 in 1981, 1,714 in 1982, 1,497 in 1983, and 2,534 in 1984. The number of cases reported during the first half of 1985 is similar to that reported during the first half of 1984 (1). As in recent years, measles was geographically restricted: 97.5% of the nation's counties were free of measles during this period.

While incidence rates during the first 26 weeks of 1984 and 1985 were comparable, there were differences in the age characteristics of patients. In 1984, persons 10-14 years of age accounted for approximately 29% of cases, compared with only 18% of cases in 1985. The incidence rate for 15- to 19-year-olds was higher in 1985. Over a third of measles patients were in this age group, due in part to the large number of outbreaks on college campuses in 1985 (4). Colleges and universities are now beginning to require evidence of immunity to measles for matriculation; this requirement should result in a decrease in measles in this population.

As the measles elimination strategy is successfully implemented, the proportion of preventable cases should decrease. The decrease in the percentage of preventable cases from 34.6% in 1984 (1) to 25.2% during the first half of 1985 is encouraging. As in 1984, preschool-aged children over 15 months of age had the highest proportion of preventable cases. Because these children are not reached by existing school laws, greater efforts need to be directed to this age group. School-aged persons accounted for the largest percentage of all preventable cases, and schools were the setting of transmission for the majority of cases. Therefore, continued enforcement of current school immunization laws is important for further reduction of measles in the United States.

References

1 CDC. Measles — United States, first 26 weeks, 1984. *MMWR* 1984;33:485-6, 491-4.
2 CDC. Classification of measles cases and categorization of measles elimination programs. *MMWR* 1982;31:707-11.
3 CDC. Measles surveillance report no. 11, 1977-1981. Atlanta, Georgia: Centers for Disease Control, 1982.
4 CDC. Measles on college campuses — United States, 1985. *MMWR* 1985;34:445-9.

TABLE 4. Reasons measles cases were classified as nonpreventable — United States, first 26 weeks, 1985*

Causes of nonpreventability	No. cases (%)		Percentage of total cases
< 15 months	242	(18.1)	13.4
Born before 1957	42	(3.1)	2.3
16 mos.-28 yrs	1,051	(77.7)	58.4
Adequately vaccinated	842	(80.1)	
Prior physician diagnosis	11	(1.0)	
Non-U.S. citizens	34	(3.2)	
Exemptions†	163	(15.5)	
Laboratory evidence of immunity	1	(0.1)	
Total	1,335	(100.0)	74.1

*Provisional data.
†Medical exemptions — 8, religious — 150, philosophic — 5.

IMPORTANT INFORMATION ABOUT POLIO AND ORAL POLIO VACCINE

Please read this carefully

OP 3/1/83

WHAT IS POLIO? Polio is a virus disease that may cause permanent crippling (paralysis) and occasionally death. There used to be thousands of cases and hundreds of deaths from polio every year in the United States. Because of the widespread use of polio vaccines, which became available beginning in the mid-1950's, polio disease has nearly been eliminated from the United States. Although thousands of cases continue to occur each year in the rest of the world, in the United States during the past 5 years there have been only 67 cases of polio reported, an average of 13 cases per year. Our success in preventing the spread of wild polio virus has been so great that most of the recent cases (approximately nine per year) have resulted from the rare side effects of oral polio vaccine (see below). Because of this fact, some people have asked why we should continue to use polio vaccine. The reason is that, even though we may not have much wild polio virus spreading here now, there is so much of it in the rest of the world that there is a great risk of its being reestablished if our children are not vaccinated.

ORAL LIVE POLIO VACCINE: Immunization with oral live polio vaccine (OPV) is one of the best ways to prevent polio. It is given by mouth starting in early infancy. Several doses are needed to provide good protection. Young children should get two or more doses in the first year of life and another dose at about 18 months of age. An additional dose is important for children when they enter school or when there is a high risk of polio, for example, during an epidemic or when traveling to a place where polio is common. The vaccine is easy to take and is effective in preventing the spread of polio. In over 90 percent of people, OPV gives protection for a long time, probably for life. Because OPV viruses live for a time in the intestinal tract of the person who is vaccinated, some of the viruses pass in the stool and can spread from the vaccinated person to those in close contact (usually household members). This may help to immunize these persons and is one of the advantages of OPV. The Immunization Practices Advisory Committee of the Public Health Service and the American Academy of Pediatrics recommend oral live polio vaccine as the preferred polio vaccine for people up to the 18th birthday.

POSSIBLE SIDE EFFECTS FROM THE VACCINE: OPV very rarely (once in about every 8.1 million doses of OPV distributed) causes paralytic polio in the person who is vaccinated. The risk may be slightly higher in adults being vaccinated and substantially higher in persons with abnormally low resistance to infection. Also very rarely (once in about every 5 million doses of OPV distributed) paralytic polio may develop in a close contact of a recently vaccinated person. Even though these risks are very low, they should be recognized. The risk of side effects from the vaccine must be balanced against the risk of the disease, both now and in the future.

(PLEASE READ OTHER SIDE)

PREGNANCY: Polio vaccine experts do not think oral polio vaccine can cause special problems for pregnant women or their unborn babies. However, doctors usually avoid giving any drugs or vaccines to pregnant women unless there is a specific need. Pregnant women should check with a doctor before taking oral polio vaccine.

WARNING—SOME PERSONS SHOULD NOT TAKE ORAL POLIO VACCINE WITHOUT CHECKING WITH A DOCTOR:

- Anyone with cancer, leukemia, or lymphoma.
- Anyone with a disease that lowers the body's resistance to infection.
- Anyone taking a drug that lowers the body's resistance to infection, such as cortisone or prednisone.
- Anyone who lives in the same household with anyone who has one of the conditions listed above.
- Anyone who is sick right now with something more serious than a cold.
- Pregnant women.
- Most persons age 18 and older because adults have a slightly bigger risk of developing paralysis from oral polio vaccine than children (However, if the risk of polio is increased-as may occur, for example, when there is an outbreak in your community-most polio experts recommend that unprotected persons receive oral polio vaccine regardless of age.)

NOTE ON INJECTABLE (KILLED) POLIO VACCINE: Besides the oral polio vaccine (OPV), there is also a killed polio vaccine (IPV) given by injection which protects against polio after several shots. This killed polio vaccine has no known risk of causing paralytic polio. Because OPV may provide lifetime protection, seems to provide stronger immunity in the intestinal tract (where infection first occurs), is simpler to administer, and is more effective in preventing the spread of polio virus than IPV, most polio experts feel that oral vaccine is more effective for controlling polio in the United States. Injectable polio vaccine is recommended for persons needing polio vaccination who have low resistance to serious infections or who live with persons with low resistance to serious infections. It may also be recommended for previously unvaccinated adults who plan to travel to a place where polio is common or for previously unvaccinated adults whose children are to be vaccinated with OPV. It is not widely used in this country at the present time, but it is available. If you would like to know more about this type of polio vaccine, or wish to receive this vaccine, please ask us.

QUESTIONS: If you have any questions about polio or polio vaccination, please ask us now or call your doctor or health department before you sign this form.

REACTIONS: If the person who received the vaccine gets sick and visits a doctor, hospital, or clinic in the 4 weeks after vaccination, please report it to the facility which provided the vaccine.

PLEASE KEEP THIS PART OF THE INFORMATION SHEET FOR YOUR RECORDS

I have read the information on this form about polio and the oral vaccine. I have had a chance to ask questions which were answered to my satisfaction. I believe I understand the benefits and risks of oral polio vaccine and request that it be given to me or to the person named below for whom I am authorized to make this request.

OP 3/1/83

INFORMATION ON PERSON TO RECEIVE VACCINE (Please Print)				
Last Name	First Name	MI	Birthdate	Age
Address				
City	County		State	Zip
X				
Signature of person to receive vaccine or person authorized to make the request.				Date

FOR CLINIC USE
Clinic Ident.
Date Vaccinated
Manuf. and Lot No.
Site of Injection

FOR DATA PROCESSING USE ONLY (OPTIONAL)

VACCINE HISTORY: PLACE CHECK ☐ IN BOX IF HISTORY PREVIOUSLY SUBMITTED

DTP:	m/d/yr	m/d/yr	m/d/yr	m/d/yr	m/d/yr	MEASLES: m/d/yr	MUMPS: m/d/yr	
POLIO:	m/d/yr	m/d/yr	m/d/yr	m/d/yr	m/d/yr	RUBELLA: m/d/yr		

IMPORTANT INFORMATION ABOUT MEASLES, MUMPS, AND RUBELLA AND MEASLES, MUMPS, AND RUBELLA VACCINES

WHAT IS MEASLES? Measles is the most serious of the common childhood diseases. Usually it causes a rash, high fever, cough, runny nose, and watery eyes lasting 1 to 2 weeks. Sometimes it is more serious. It causes an ear infection or pneumonia in nearly 1 out of 10 children who get it. Approximately 1 child out of every 1,000 who get measles has an inflammation of the brain (encephalitis). This can lead to convulsions, deafness, or mental retardation. About 2 children in every 10,000 who get measles die from it. Measles can also cause a pregnant woman to have a miscarriage or give birth to a premature baby.

Before measles vaccine shots were available, there were hundreds of thousands of cases and hundreds of deaths each year. Nearly all children got measles by the time they were 15. Now, wide use of measles vaccine has nearly eliminated measles from the United States. However, if children are not vaccinated they have a high risk of getting measles, either now or later in life.

WHAT IS MUMPS? Mumps is a common disease of children. Usually it causes fever, headache, and inflammation of the salivary glands, which causes the cheeks to swell. Sometimes it is more serious. It causes a mild inflammation of the coverings of the brain and spinal cord (meningitis) in about 1 child in every 10 who get it. More rarely, it can cause inflammation of the brain (encephalitis) which usually goes away without leaving permanent damage. Mumps can also cause deafness. About 1 out of every 4 adolescent or adult men who get mumps develops painful inflammation and swelling of the testicles. While this condition usually goes away, on rare occasions it may cause sterility.

Before mumps vaccine shots were available, there were more than 150,000 cases each year. Now, because of the wide use of mumps vaccine, the number of cases of mumps is much lower. However, if children are not vaccinated, they have a high risk of getting mumps.

WHAT IS RUBELLA? Rubella is also called German measles. It is a common disease of children and may also affect adults. Usually it is very mild and causes a slight fever, rash, and swelling of glands in the neck. The sickness lasts about 3 days. Sometimes, especially in adult women, there may be swelling and aching of the joints for a week or two. Very rarely, rubella can cause inflammation of the brain (encephalitis) or cause a temporary bleeding disorder (purpura).

The most serious problem with rubella is that if a pregnant woman gets this disease, there is a good chance that she may have a miscarriage or that the baby will be born crippled, blind, or with other defects. The last big rubella epidemic in the United States was in 1964. Because of that epidemic, about 25,000 children were born with serious problems such as heart defects, deafness, blindness, or mental retardation because their mothers had rubella during the pregnancy.

Before rubella vaccine shots were available, rubella was so common that most children got the disease by the time they were 15. Now, because of the wide use of rubella vaccine, the number of cases of rubella is much lower. However, if children are not vaccinated, they have a high risk of getting rubella and possibly exposing a pregnant woman to the disease. If an unvaccinated woman later becomes pregnant and catches rubella, she may have a defective baby.

Since rubella is a mild illness, many women of childbearing age do not recall if they had rubella as a child. A simple blood test can show whether a person is immune to rubella or is not protected against the disease. Overall, about one in five women of childbearing age is not protected against rubella.

Please read this carefully

MMR 3/1/83

(PLEASE READ OTHER SIDE.)

MEASLES, MUMPS, AND RUBELLA VACCINES: The vaccines are given by injection and are very effective. Ninety percent or more of people who get the shot will have protection, probably for life. Since protection is not as likely to occur if the vaccines are given very early in life, these vaccines should be given to children after their first birthday; measles vaccine should be given at 15 months of age or older. Measles, mumps, and rubella vaccines can be given one at a time or in a combined vaccine (measles-rubella [MR], measles-mumps-rubella [MMR]) by a single shot. If they are given in combined vaccine, they should be given at 15 months of age or older.

Experts recommend that adolescents and adults—especially women of childbearing age—who are not known to be immune to rubella should receive rubella vaccine (or MMR if they might also be susceptible to measles or mumps). Women should not receive the shot if they are pregnant or might become pregnant within 3 months. There is no known risk in being vaccinated against any or all three of these diseases if you are already immune to any of them.

POSSIBLE SIDE EFFECTS FROM THE VACCINES: About 1 out of every 5 children will get a rash or slight fever lasting for a few days, 1 or 2 weeks after getting measles vaccine. Occasionally there is mild swelling of the salivary glands after mumps vaccination.

About 1 out of every 7 children who get rubella vaccine will get a rash or some swelling of the glands of the neck 1 or 2 weeks after the shot. About 1 out of every 20 children who get rubella vaccine will have some aching or swelling of the joints. This may happen anywhere from 1-3 weeks after the shot. It usually lasts only 2 or 3 days. Adults are more likely to have these problems with their joints—as many as 1 in 4 may have them. Other temporary side effects, such as pain, numbness, or tingling in the hands and feet have also occurred but are very uncommon.

Although experts are not sure, it seems that *very rarely* children who get these vaccines may have a more serious reaction, such as inflammation of the brain (encephalitis), convulsions with fever, or nerve deafness.

With any vaccine or drug, there is a possibility that allergic or other more serious reactions or even death could occur.

WARNING—SOME PERSONS SHOULD *NOT* TAKE THESE VACCINES WITHOUT CHECKING WITH A DOCTOR:

- Anyone who is sick right now with something more serious than a cold.
- Anyone who had an allergic reaction to eating eggs so serious that it required medical treatment (does not apply to rubella vaccine).
- Anyone with cancer, leukemia, or lymphoma.
- Anyone with a disease that lowers the body's resistance to infection.
- Anyone taking a drug that lowers the body's resistance to infection (such as cortisone, prednisone or certain anticancer drugs)
- Anyone who has received a gamma globulin (immune globulin) within the preceding 3 months.
- Anyone who had an allergic reaction to an antibiotic called neomycin so serious that it required medical treatment.

PREGNANCY: Measles, mumps, and rubella vaccines are not known to cause special problems for pregnant women or their unborn babies. However, doctors usually avoid giving any drugs or vaccines to pregnant women unless there is a specific need. To be safe, pregnant women should not get these vaccines. A woman who gets any of these vaccines should wait 3 months before getting pregnant.

Vaccinating a child whose mother is pregnant is not dangerous to the pregnancy.

QUESTIONS: If you have any questions about measles, mumps, or rubella vaccination, please ask us now or call your doctor or health department before you sign this form.

REACTIONS: If the person who received the vaccine gets sick and visits a doctor, hospital, or clinic in the 4 weeks after vaccination, please report it to the facility which provided the vaccine.

PLEASE KEEP THIS PART OF THE INFORMATION SHEET FOR YOUR RECORDS

I have read the information on this form about measles, mumps, and rubella and measles, mumps, and rubella vaccines. I have had a chance to ask questions which were answered to my satisfaction. I believe I understand the benefits and risks of measles, mumps and rubella vaccines and request that the vaccine checked below be given to me or to the person named below for whom I am authorized to make this request.

VACCINE TO BE GIVEN: ☐ *Measles* ☐ *Mumps* ☐ *Rubella* ☐ *Measles-Rubella* ☐ *Measles-Mumps-Rubella* **MMR 3/1/83**

INFORMATION ON PERSON TO RECEIVE VACCINE (Please Print)

Last Name _____ First Name _____ MI _____ Birthdate _____ Age _____

Address _____

City _____ County _____ State _____ Zip _____

X _____

Signature of person to receive vaccine or person authorized to make the request _____ Date _____

FOR CLINIC USE

Clinic Ident. _____

Date Vaccinated _____

Manufacturer and Lot No. _____

Site of injection _____

FOR DATA PROCESSING USE ONLY (OPTIONAL)

VACCINE HISTORY: ☐ PLACE CHECK IN BOX IF HISTORY PREVIOUSLY SUBMITTED

DTP: _____ _____ _____ _____ _____ MEASLES: _____ MUMPS: _____
m/d/yr m/d/yr m/d/yr m/d/yr m/d/yr m/d/yr m/d/yr

POLIO: _____ _____ _____ _____ _____ RUBELLA: _____
m/d/yr m/d/yr m/d/yr m/d/yr m/d/yr m/d/yr

IMPORTANT INFORMATION ABOUT DIPHTHERIA, TETANUS, AND PERTUSSIS AND DTP, DT, AND Td VACCINES

Please read this carefully

DTP 2/1/86

WHAT IS DIPHTHERIA? Diphtheria is a very serious disease which can affect people in different ways. It can cause an infection in the nose and throat which can interfere with breathing. It can also cause an infection of the skin. Sometimes it causes heart failure or paralysis. About 1 person out of every 10 who get diphtheria dies of it.

WHAT IS TETANUS? Tetanus, or lockjaw, results when wounds are infected with tetanus bacteria, which are often found in dirt. The bacteria in the wound make a poison which causes the muscles of the body to go into spasm. Four out of every 10 persons who get tetanus die of it.

WHAT IS PERTUSSIS? Pertussis, or whooping cough, causes severe spells of coughing which can interfere with eating, drinking, and breathing. In the United States, more than 75 percent of reported pertussis cases occur in children younger than 5 years. Pertussis is a more serious disease in young children and more than half of the children less than 1 year of age reported to have pertussis are hospitalized. In recent years, an average of 1,700 cases of pertussis have been reported each year in the United States. Complications occur in a substantial proportion of reported cases. Pneumonia occurs in one of every four children with pertussis. For every 1,000 reported pertussis cases, 22 develop convulsions and/or have more severe problems of the brain. In recent years, an average of eight deaths due to pertussis occurred annually.

Before vaccines were developed, these three diseases were all very common and caused a large number of deaths each year in the United States. If children are not vaccinated, the risk of getting these diseases will go back up again.

DTP, DT, AND Td VACCINES: Immunization with DTP vaccine is one of the best ways to prevent these diseases. DTP vaccine is actually three vaccines combined into one shot to make it easier to get protection. The United States Public Health Service and the American Academy of Pediatrics recommend DTP vaccine be used in children up to their seventh birthday. The vaccine is given by injection starting early in infancy. At least three shots are needed to provide initial protection. Young children should get three doses in the first year of life and a fourth dose at about 18 months of age. A booster shot is important for children who are about to enter school and should be given between their fourth and seventh birthdays. The vaccine is very effective at preventing tetanus—over 95 percent of those who get the vaccine are protected if the recommended number of shots is given. Although the diphtheria and pertussis parts of the vaccine are not quite as effective, they still prevent most children from getting disease and they make the disease milder for those who do get it.

Because pertussis is not very common or severe in older children, those 7 years of age and older should take a vaccine that does not contain the pertussis part. Also, because reactions to the diphtheria part of the vaccine may be more common in older children, those 7 years of age and older should take a form of the vaccine that has a lower concentration of the diphtheria part. This vaccine which contains no pertussis part and a lower concentration of the diphtheria part is called Td vaccine. Boosters with the Td vaccine should be received every 10 years throughout life.

(PLEASE READ OTHER SIDE)

DEFERRAL OF DTP IMMUNIZATION: Children who have had a serious reaction to previous DTP shots should not receive additional pertussis vaccine (see WARNING). A preparation called DT vaccine is available for them which does not contain the pertussis part. Also, children who have previously had a convulsion or are suspected to have a problem of the nervous system should not receive DTP vaccine until a full medical evaluation has been made.

POSSIBLE SIDE EFFECTS FROM THE VACCINE: With DTP vaccine, most children will have a slight fever and be irritable within 2 days after getting the shot. One half of children develop some soreness and swelling in the area where the shot was given. More serious side effects can occur. A temperature of 105°F or greater may follow 1 out of 330 DTP shots. Continuous crying lasting 3 or more hours may occur after 1 in every 100 shots and unusual, high-pitched crying may occur after 1 in every 900 shots. Convulsions or episodes of limpness and paleness may each occur after 1 in every 1,750 shots. Children who have previously had a convulsion may be more likely to have another one after pertussis shots. Rarely, about once in every 110,000 shots, other more severe problems of the brain may occur, and permanent brain damage may occur about once in every 310,000 shots. Side effects from DT or Td vaccine are not common and usually consist only of soreness and slight fever. As with any drug or vaccine, there is a rare possibility that allergic or more serious reactions or even death could occur.

Although some people have questioned whether DTP shots might cause Sudden Infant Death Syndrome (SIDS), in careful studies DTP shots have not been shown to cause SIDS.

PREGNANCY: Babies born under unsanitary conditions to unimmunized women have a risk of developing tetanus during the newborn period (neonatal tetanus). Neonatal tetanus can be prevented by immunization of adult women. Women who have not received Td earlier and who are thought to be at risk of delivering their babies under unsanitary conditions should be immunized during pregnancy.

Td is not known to cause special problems for pregnant women or their unborn babies. Doctors usually do not recommend giving any drugs or vaccines to pregnant women unless there is a specific need. Pregnant women who need Td should receive it, preferably during the second and/or third trimesters.

WARNING—SOME PERSONS SHOULD *NOT* TAKE THESE VACCINES WITHOUT CHECKING WITH A DOCTOR:

- Anyone who is sick right now with something more serious than a cold.
- Anyone who has had a convulsion or is suspected to have a problem of the nervous system.
- Anyone who has had a serious reaction to DTP, DT, or Td shots before, such as: an allergic reaction to any vaccine component; a temperature of 105°F or greater; an episode of limpness and paleness; prolonged continous crying; an unusual, high-pitched cry; or a convulsion or other more severe problem of the brain.
- Anyone taking a drug or undergoing a treatment that lowers the body's resistance to infection, such as: cortisone, prednisone, certain anticancer drugs, or irradiation.

QUESTIONS: If you have any questions about diphtheria, tetanus, or pertussis or DTP, DT, or Td vaccination, please ask us now or call your doctor or health department before you sign this form.

REACTIONS: If the person who received the vaccine develops a temperature of 105°F or greater, continuous crying lasting 3 or more hours, an unusual high-pitched cry, a convulsion, an episode of limpness and paleness, or a severe problem of the brain, the person should be evaluated promptly by a doctor.

If the person who received the vaccine gets sick and visits a doctor, hospital, or clinic in the 4 weeks after vaccination, please report it to the facility which provided the vaccine.

PLEASE KEEP THIS PART OF THE INFORMATION SHEET FOR YOUR RECORDS

I have read the information on this form about diphtheria, tetanus, and pertussis and DTP, DT, and Td vaccines. I have had a chance to ask questions which were answered to my satisfaction. I believe I understand the benefits and risks of DTP, DT, and Td vaccines and request that the vaccine checked below be given to me or to the person named below for whom I am authorized to make this request.

VACCINE TO BE GIVEN: ☐ DTP ☐ DT ☐ Td

DTP 2/1/93

INFORMATION ABOUT PERSON TO RECEIVE VACCINE (Please Print)				
Last Name	First Name	MI	Birthdate	Age
Address				
City	County		State	Zip
X				
Signature of person to receive vaccine or person authorized to make the request.				Date

FOR CLINIC USE
Clinic Ident.
Date Vaccinated
Manuf. and Lot No.
Site of Injection

FOR DATA PROCESSING USE ONLY (OPTIONAL)

VACCINE HISTORY: PLACE CHECK ☐ IN BOX IF HISTORY PREVIOUSLY SUBMITTED

DTP:	m/d/yr	m/d/yr	m/d/yr	m/d/yr	m/d/yr	MEASLES: m/d/yr	MUMPS: m/d/yr	
POLIO:	m/d/yr	m/d/yr	m/d/yr	m/d/yr	m/d/yr	RUBELLA: m/d/yr	HAEMOPHILUS b:	

BILL SHEFFIELD, GOVERNOR

DEPT. OF HEALTH AND SOCIAL SERVICES

DIVISION OF PUBLIC HEALTH
SECTION OF COMMUNICABLE DISEASE CONTROL

3601 "C" STREET, SUITE 576
POUCH 6333
ANCHORAGE, AK 99502-0333
(907) 561-4235

November 14, 1986

Ms. Shannon Kohler
Alaska Chapter-DPT
Box 1746
Soldotna, AK 99669

Dear Ms. Kohler:

Thank you for the information relative to the pertussis poster containing incorrect information. We are not aware of any state-wide department offices displaying such a poster.

The "Dear Health Care Provider" contains information which has been in existence for at least two years and is considered common knowledge by most health care providers who administer vaccine. However, it maybe appropriate to reiterate the information in an upcoming edition of the Epidemiology Bulletin (a news bulletin sent to health care providers and other interested parties). Also, we will be rewriting the immunization standing orders for the Public Health Nurses and, if not already part of their standing orders, we will include this important information.

The State does not have any specific regulations regarding the reporting of adverse reactions following immunizations. Health care provders who administer vaccines are encouraged to report possible adverse reactions to this office. This is a passive surveillance system which relies on the integrity of the health care providers to comply.

The answers to your remaining questions are as follows:

1. Report Gathering

   A. How are adverse reactions gathered from parents? from public health officials administering vaccine? from doctors?

      Parents are to notify the provider of the vaccine if the vaccinee visits a doctor, hospital, or clinic within 4 weeks of vaccination, as requested on every Important Information Form. A public provider who is made aware of a possible adverse reaction completes the MSAEFI report form and submits it to this office. A private physician who is made aware of a possible adverse reaction notifies this office and the MSAEFI Coordinator completes the MSAEFI report form.

B. What is the estimated rate of compliance?

C. How exactly is the rate of compliance determined?

No estimated rate of compliance is determined.

2. Handling Reports

A. Once a report is received, where and how is it recorded?

All submitted MSAEFI report forms are entered onto a MSAEFI report form log sheet by the MSAEFI Coordinator. All submitted MSAEFI report forms which meet the minimal criteria for submission to the Centers for Disease Control are forwarded.

B. Is the original or copy of report kept by State office?

A typed carbon copy is retained by the State office.

C. Is the original or copy of report sent to the National Center of Disease Control (CDC) in Atlanta Georgia?

A typed copy is forwarded to the CDC.

3. Approximately how many adverse reaction reports does your office receive per year from public health officials?

1985 - 12 (2 of which were military)
1986 - 9

from doctors?

1985 - 3
1986 - 1

from parents?

1985 - 0
1986 - 0

(The numbers listed above indicate adverse reaction reports forwarded to the CDC, not the number received by this office.)

B. What are the symptoms and diagnosis included in reports?

See enclosed MSAEFI report form.

And, finally, your last request to "send me a copy of the annual Alaska State reports regarding immunizations and reactions that were sent to Atlanta, Georgia CDC in 1984 and 1985," will have to be more specific.

There are no annual reaction reports, however, there a quite a few immunization reports sent to the CDC quarterly and annually by this office. If the specific information you want is available, we will send it to you.

Sincerely,

Michael Klatt

Michael Klatt, Manager
Alaska Immunization Program

Robert I. Fraser, M.D. Chief
Sec. of Comm. Disease Control

MK+RIF:ew

Enclosure

cc: Elizabeth Ward, Director
Division of Public Health

STATE OF ALASKA

BILL SHEFFIELD, GOVERNOR

DEPT. OF HEALTH AND SOCIAL SERVICES

DIVISION OF PUBLIC HEALTH
SECTION OF COMMUNICABLE DISEASE CONTROL

3601 "C" STREET, SUITE 576
POUCH 6333
ANCHORAGE, AK 99502-0333
(907) 561-4235

May 1, 1986

The information you requested about DTP vaccine and whooping cough was not easily retrievable. The major reason being that I have only been on the job three months, therefore, I didn't know who to ask or where to look. However, this is what I have found.

1. There were five cases of whooping cough in 1984 and 30 cases in 1985.

2. Four of the five cases were confirmed in 1984 and nine of the 30 cases were confirmed in 1985.

3. A total of four of the 35 cases were hospitalized with no deaths.

4.

Age	1984	1985
unknown	0	4
<1	2	10
1	1	6
2	0	4
5-9	0	2
10-19	0	3
20-24	0	1
25-29	1	0
30-39	1	0

Approximately half of the cases had received pertussis vaccine at some point in their life , however, whether they were appropriately immunized for age I am unable to ascertain.

5. The parents/guardians of recipients who see a physician or who are hospitalized within one month of an immunization are supposed to notify the Alaska Immunization Program. When I receive notification of an adverse event following an immunization, I contact the parents/guardians, the immunization provider, and the attending physician. It is the physician's responsibility to determine whether or not the patient's problems are vaccine-related. All vaccine-related adverse reactions are documented on an official report form and sent to the Centers for Disease Control in Atlanta, Georgia.

I hope the enclosures are of help to you.

Sincerely,

Michael Klatt

Michael Klatt, Manager
Alaska Immunization Program

MK:db

(For Adult Use) is recommended.[1-8]

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Aluminum Phosphate Adsorbed, is available in vials of 7.5 ml. Product 1948-33

STORAGE

Keep between 2 and 8° C (35-46° F). DO NOT FREEZE.

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Lederle

LABORATORIES DIVISION
American Cyanamid Company, Pearl River, N.Y. 10965

REV. 11/84

16042
DX12

DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE ADSORBED TRI-IMMUNOL®

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, TRI-IMMUNOL® Lederle, is a combination of *Purogenated* Diphtheria Toxoid Aluminum Phosphate-Adsorbed, *Purogenated* Tetanus Toxoid Aluminum Phosphate-Adsorbed, and Pertussis Vaccine.

DESCRIPTION

The diphtheria toxin is produced according to the method of Mueller and Miller and is detoxified by use of formaldehyde. The tetanus toxin is produced by the method of Mueller and Miller and is detoxified by the use of formaldehyde. The toxoids are refined by the Pillemer alcohol fractionation method and are diluted with a solution containing potassium phosphate monobasic, sodium phosphate dibasic, glycine, and thimerosal (mercury derivative) as a preservative. Pertussis Vaccine is prepared by growing Phase I *B. pertussis* in a modified Cohen-Wheeler broth containing acid hydrolysate of casein. The *B. pertussis* culture is harvested, inactivated, and then suspended in a solution containing potassium phosphate monobasic, sodium phosphate dibasic, sodium chloride, and thimerosal (mercury derivative) as a preservative and is then combined with the refined Diphtheria and Tetanus Toxoids in physiological saline (NaCl) diluent containing thimerosal (mercury derivative) as a preservative. The final concentration of thimerosal (mercury derivative) in the combined vaccine is 1:10,000. The aluminum content of the final product does not exceed 0.80 mg per 0.5 ml dose.

The total immunizing dose contains 12 units of pertussis vaccine.

The primary immunization against diphtheria, tetanus, and pertussis consists of four 0.5 ml doses when administered as recommended.[1-8]

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, tetanus, and pertussis during infancy and childhood has been a routine practice in the United States since the late 1940's. It has played a major role in markedly reducing the incidence of cases and deaths from each of these diseases.

Diphtheria is primarily a localized and generalized intoxication caused by diphtherial toxin, an extracellular protein metabolite of toxinogenic strains of *Corynebacterium diphtheriae*. While the incidence of diphtheria has decreased from about 20 cases per 100,000 population before the general use of diphtheria toxoid[1-3] to about 56 cases reported between 1976 and 1981, the ratio of fatalities to attack rate has remained constant at about 5%-10%. The highest case fatality rates are in the very young and the elderly. Diphtheria toxoid induces antitoxin. Following adequate immunization with diphtheria toxoid is thought to protect for at least 10 years.[1]

It significantly reduces both the risk of developing diphtheria and the severity of clinical illness. It does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or on the skin.[1] A serum level ≥0.01 toxin neutralization units/ml is generally considered protective.[1]

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin elaborated by *Clostridium tetani*. The incidence of tetanus has dropped dramatically with the routine use of tetanus toxoid, remaining relatively constant over the last decade at about 100 cases reported annually. Spores of *C. tetani* are ubiquitous and there is essentially no natural immunity to tetanus toxin. Thus, universal primary immunization with tetanus toxoid with subsequent maintenance of adequate antitoxin levels by means of timed boosters is necessary to protect all age groups.[1] Tetanus toxoid is highly effective, with a failure rate in fully immunized persons of less than 4 per 100 million.[1] Protective levels of serum antitoxin (≥0.01 toxin neutralization units/ml)[4] are achieved which persist for at least 10 years after full immunization.[1]

Pertussis is a disease of the respiratory tract caused by *Bordetella pertussis*. This gram-negative coccobacillus produces an array of biologically active components that escape from the site of infection and produce systemic effects, including an endotoxin-related febrile response, attenuation of the host's febrile and inflammatory responses, lymphocytosis, leukocytosis, effects on glucose homeostasis, and possible neurotoxicity. The role of each of the different components in the pathogenesis of and immunity to pertussis is not well understood.

Pertussis is a highly communicable disease which, unique for a bacterial disease, has an attack rate in unimmunized populations of over 90%.[3] As a result of immunization with pertussis vaccine, the number of reported cases and associated mortality has de-

clined from about 120,000 cases and 1,100 deaths in 1950[4] to an annual average of abou 2,300 cases and 10 fatalities over the last 10 years.[1] Accurate data do not exist as bacteriological confirmation of pertussis can be obtained in less than half of the cases reported. Illnesses from *B. pertussis* occur in infants and young children. two-thirds of reported deaths occur in children less than one year old. Older children and adults in whom classic signs are often absent, may go undiagnosed and serve as reservoirs of disease.[1]

Evidence of the efficacy of pertussis vaccine can be provided by the recent British experience, where a reduction in the number of immunized individuals from 79% in 1973, to 31% in 1978 resulted in an epidemic of 102,500 pertussis cases and 36 deaths between late 1977 and 1980, and 1,440 cases per week reported during the winter of 1981-82. A similar situation occurred in Japan.[4]

Because the incidence and severity of pertussis decrease with age, routine pertussis immunization is not recommended for persons 7 years of age or older.[1]

INDICATION AND USAGE

Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed is indicated for active immunization of infants and children through 6 years of age against diphtheria, tetanus, and pertussis.[1-3]

CONTRAINDICATIONS

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS A CONTRAINDICATION TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF CENTRAL NERVOUS SYSTEM DISORDERS.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that pertussis vaccine should be withheld when a previous dose has been followed by convulsion, encephalitis, focal neurological signs, or collapse. Nor should infants who experience excessive somnolence, excessive screaming (persistent crying or screaming for three or more hours duration) or temperature more than 105° F (40.5° C) receive additional doses of the vaccine.[1]

The Immunization Practices Advisory Committee (ACIP) of the U.S. Public Health Service recommends that hypersensitivity to vaccine components, presence of an evolving neurologic disorder, or a history of a severe reaction (usually within 48 hours) following a previous dose all remain definitive contraindications to the receipt of pertussis vaccine. Severe reactions include collapse or shock, persistent screaming episode, temperature 40.5° C (105° F) or greater, convulsion(s) with or without accompanying fever, severe alterations of consciousness, generalized and/or local neurologic signs, or systemic allergic reactions.[1]

Immunosuppressive therapy, including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents may result in aberrant responses to active immunization procedures. Administration should be deferred in individuals receiving such therapy.

The clinical judgement of the attending physician should prevail at all times.

Elective immunization of patients over the age of 6 months should be deferred during an outbreak of poliomyelitis.

WARNING

THIS PRODUCT IS NOT RECOMMENDED FOR IMMUNIZING PERSONS AFTER THEIR SEVENTH BIRTHDAY. DO NOT ATTEMPT ROUTINE IMMUNIZATION IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF CENTRAL NERVOUS SYSTEM DISORDERS. SHOULD ANY SYMPTOMATOLOGY RELATED TO NEUROLOGICAL DISORDERS DEVELOP FOLLOWING ADMINISTRATION, DO NOT ATTEMPT FURTHER ADMINISTRATION OF PERTUSSIS VACCINE. CONVULSION, ENCEPHALITIS, FOCAL NEUROLOGIC SIGNS, COLLAPSE, SHOCK, EXCESSIVE SCREAMING (PERSISTENT CRYING OR SCREAMING FOR THREE OR MORE HOURS DURATION), EXCESSIVE SOMNOLENCE, SEVERE ALTERATION OF CONSCIOUSNESS, SYSTEMIC ALLERGIC REACTIONS OR TEMPERATURE MORE THAN 105° F (40.5° C) ARE CONTRAINDICATIONS FOR ANY FURTHER USE OF PERTUSSIS VACCINE.

If such disorders are found, the infants or children should be given diphtheria and tetanus toxoids (DT) instead of DTP. If DT is used, three doses at least 4 weeks apart, followed by a fourth dose 6-12 months later, are recommended for infants. For children 1 year of age or older, two doses of DT at least 4 weeks apart followed by a third dose 6-12 months later, are recommended.[1]

The occurrence of sudden-infant-death syndrome (SIDS) has been reported following administration of DTP.[10-11] A causal relationship between DTP immunization and the syndrome has not been established.[12-14]

Prior to administration of this vaccine, health care personnel should inform the parent, guardian, or other responsible adult of the benefits and risks to the child of DTP vaccine. For recent information about the estimated range of risks of severe reactions following DTP administration, consult references 1, 15, 16, 17, 18, and 21.

DTP should not be given to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

If the vaccine is used in persons receiving immunosuppressive therapy, the expected antigenic response may not be obtained.

Special care should be taken so the injection is not made into a blood vessel.

PRECAUTIONS

A. *General*

1. This product should be used for the age group between 2 months and the 7th birthday.
2. A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.
3. *Since this product contains both a bacterial suspension and an adjuvant, shake vigorously before withdrawing each dose from multiple dose vials.*
4. Before the injection of any biological, the physician should take all precautions known for prevention of allergic or any other side reactions. This should include: A review of the patient's history regarding possible sensitivity; the ready availability of epinephrine 1:1000 and other appropriate agents used for control of immediate allergic reactions; and a knowledge of the recent literature pertaining to use of the biological concerned, including the nature of side effects and adverse reactions that may follow its use.

B. *Information for Parent*

1. Prior to administration of any dose of DTP, the parent or guardian should be asked about the recent health status of the infant or child to be injected.
2. WHEN AN INFANT OR CHILD IS RETURNED FOR THE NEXT DOSE IN THE SERIES, THE PARENT SHOULD BE QUESTIONED CONCERNING OCCURRENCE OF ANY SYMPTOM AND/OR SIGNS OF AN ADVERSE REACTION AFTER THE PREVIOUS DOSE (SEE CONTRAINDICATIONS, ADVERSE REACTIONS).

ADVERSE REACTIONS

Local reactions, manifested by erythema and induration with or without tenderness, are common after administration of DTP. Such local reactions are usually self-limited and require no therapy. A nodule may be palpable at the injection site for a few weeks.

Abscess formation at the site of injection has been reported.[1,19,20] Cervical lymphadenopathy has been reported following DTP injections into the arm.[19]

Mild to moderate temperature elevations frequently follow DTP administration and are often accompanied by irritability, drowsiness, vomiting, and anorexia.[1,10,19] Approximately 50% of DTP recipients will develop temperature elevations ≥ 38° C (100.4° F) after one or more doses of the series, approximately 6% ≥ 39° C (102.2° F), and approximately 1.5% ≥ 40° C (104° F). Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses.[19]

SIGNIFICANT REACTIONS ATTRIBUTED TO THE PERTUSSIS VACCINE COMPONENT HAVE BEEN: HIGH FEVER OF 40.5° C (105° F), A TRANSIENT SHOCK-LIKE EPISODE, EXCESSIVE SCREAMING (PERSISTENT CRYING OR SCREAMING FOR THREE OR MORE HOURS DURATION), SOMNOLENCE, CONVULSIONS, AND ENCEPHALOPATHY. THESE REACTIONS HAVE BEEN REPORTED TO OCCUR RARELY FOLLOWING THE INJECTION OF THIS PRODUCT AND THEY MAY BE FATAL OR RESULT IN PERMANENT DAMAGE TO THE CENTRAL NERVOUS SYSTEM. PERTUSSIS VACCINE HAS BEEN ASSOCIATED WITH A GREATER PROPORTION OF ADVERSE REACTIONS THAN MANY OTHER CHILDHOOD IMMUNIZATIONS.[1,19] SHOULD SYMPTOMATOLOGY REFERABLE TO THE CENTRAL NERVOUS SYSTEM DEVELOP FOLLOWING ADMINISTRATION, FURTHER IMMUNIZATION WITH THIS PRODUCT IS CONTRAINDICATED (SEE CONTRAINDICATIONS). SUCH REACTIONS ALMOST ALWAYS APPEAR WITHIN 24 TO 48 HOURS AFTER INJECTION, BUT HAVE BEEN THOUGHT TO OCCUR AFTER AN INTERVAL AS LONG AS SEVEN DAYS.

NEUROLOGICAL COMPLICATIONS FOLLOWING TETANUS TOXOID ADMINISTRATION, SUCH AS PARALYSIS OF THE RADIAL NERVE,[21] RECURRENT PHARYNGEAL NERVE,[22] COCHLEAR LESION,[23] BRACHIAL PLEXUS NEUROPATHY,[21,24] AND A CASE OF DIFFICULTY IN SWALLOWING, ACCOMMODATION PARESIS, AND EEG DISTURBANCES[25] HAVE BEEN REPORTED. IN THE DIFFERENTIAL DIAGNOSIS OF POLYRADICULONEUROPATHIES FOLLOWING ADMINISTRATION OF TETANUS TOXOID, TETANUS TOXOID SHOULD BE CONSIDERED AS A POSSIBLE ETIOLOGY.[21]

DOSAGE AND ADMINISTRATION

Shake vigorously before withdrawing each dose from the multiple dose vials.

Before injection, the skin over the site to be injected should be cleansed and prepared with a suitable germicide. After insertion of the needle, aspirate to help avoid inadvertent injection into a blood vessel. Expel the dose slowly and terminate the dose with a small bubble of air (0.1 to 0.2 ml).

The basic immunizing course for infants and children through 6 years of age consists of three doses of 0.5 ml each at 4- to 8-week intervals, followed by a fourth dose of 0.5 ml approximately one year after the third dose.

It is recommended that active immunization against diphtheria, tetanus, and pertussis be started at 2 months of age.[1,3] All doses should be injected intramuscularly, preferably into the mediateral muscles of the thigh or deltoid, with care to avoid major peripheral nerve trunks.

Interruption of the recommended schedule with a delay between doses does not interfere with the final immunity achieved; nor does it necessitate starting the series over again, regardless of the length of time elapsed between doses.[1]

A recall (booster) dose of 0.5 ml is indicated at age 4-6 years, preferably prior to entrance into kindergarten or elementary school. However, if the fourth dose of the basic immunizing series was administered after the fourth birthday, a recall (booster) of DTP prior to school entry is not considered necessary.[1]

For either basic or recall (booster) immunization against tetanus and diphtheria of individuals 7 years of age and older, the use of Tetanus and Diphtheria Toxoids Adsorbed

STORAGE

To maintain potency it is necessary to store this vaccine at a temperature which will maintain ice continuously in a solid state. This vaccine may remain fluid at temperatures above -14° C (+7° F) because of its sorbitol content. If frozen, the vaccine must be completely thawed prior to use. An *unopened* container of vaccine that has been frozen and then is thawed may be carried through a maximum of 10 freeze-thaw cycles, provided the temperature does not exceed 8° C (46° F) during the periods of thaw, and provided the total cumulative duration of thaw does not exceed 24 hours. If the 24-hour period is exceeded, the vaccine then must be used within 30 days, during which time it must be stored at a temperature between 2-8° C (36-46° F).

DISCLAIMER OF REPRESENTATIONS AND WARRANTIES

This vaccine has been produced and tested in accordance with the regulations of the United States Food and Drug Administration for the production of Poliovirus Vaccine, Live, Oral Trivalent. The manufacturer makes no representation or warranty, expressed or implied, with respect to the merchantability or fitness for use of this vaccine other than that the vaccine has been produced in accordance with the standards for its production prescribed by the United States Food and Drug Administration and applicable thereto at the time of its release by the manufacturer. While the use of this preparation and other measures described herein are consistent with accepted standards of medical practice, their use as described cannot be expected necessarily to assure a specific result.

HOW SUPPLIED

2084-08 - 10 (0.5 ml) DISPETTES® Disposable Pipettes
2084-12 - 50 (0.5 ml) DISPETTES®

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LEDERLE LABORATORIES DIVISION
American Cyanamid Company, Pearl River, N.Y. 10965

REV. 12/82

80:12

POLIOVIRUS VACCINE, LIVE, ORAL TRIVALENT ORIMUNE®

0.5 ml Dose

Contains Sorbitol

SABIN STRAINS TYPES 1, 2 and 3

FOR ORAL ADMINISTRATION - NOT FOR INJECTION

DESCRIPTION

Manufacture and Composition: ORIMUNE® TRIVALENT VACCINE is a mixture of three types of attenuated polioviruses which have been propagated in cercopithecus monkey kidney cell culture. The cells are grown in the presence of Eagle's Basal Medium consisting of Earle's Balanced Salt Solution containing amino acids, antibiotics and calf serum. After cell growth, the medium is removed and replaced with fresh medium containing the inoculating virus but no calf serum. The final vaccine is diluted with a modified cell culture maintenance medium containing sorbitol. Each dose (0.5 ml) contains less than 25 micrograms of each of the antibiotics, streptomycin and neomycin.

The potency is expressed in terms of the amount of virus contained in the recommended dose as tissue culture infective doses ($TCID_{50}$). The human dose of vaccine containing all three virus types shall be constituted to have infectivity titers in the final container material of $10^{5.4}$ to $10^{6.4}$ for Type 1, $10^{4.5}$ to $10^{5.5}$ for Type 2 and $10^{5.2}$ to $10^{6.2}$ for Type 3.[1]

Color Change: This vaccine contains phenol red as a pH indicator. The usual color of the vaccine is pink, although some containers of vaccine, shipped or stored in dry ice, may exhibit a yellow coloration due to the very low temperature or possible absorption of carbon dioxide. The color of the vaccine prior to use (red -pink - yellow) has no effect on the virus or efficacy of the vaccine.

INDICATIONS AND USAGE

The purpose of administering any attenuated, live, virus vaccine is to stimulate the body mechanism to produce an active immunity by simulating the natural infection without producing untoward symptoms of the disease. To accomplish this with live poliovirus vaccine, it is necessary for the virus to multiply in the intestinal tract. A primary series of this vaccine is designed to produce an antibody response to poliovirus Types 1, 2 and 3. This response is comparable to the immunity induced by the natural disease. The antibodies thus formed help protect the individual against clinical poliomyelitis infection by any of the three types of poliovirus. When used in the prescribed manner for primary immunization, type specific neutralizing antibodies will be induced in 90% or more of susceptibles.

This vaccine is indicated for use in the prevention of poliomyelitis caused by poliovirus Types 1, 2 and 3.

Infants starting at six to twelve weeks of age, *all unimmunized children* and *adolescents* through age 18 are the usual candidates for routine prophylaxis.

The Immunization Practices Advisory Committee (IPAC) of the Public Health Service states that trivalent oral poliovirus vaccine (TOPV) and inactivated poliovirus vaccine (IPV) are both effective in preventing poliomyelitis. TOPV is the vaccine of choice for primary immunization of children in the United States when the benefits and risks for the entire population are considered. TOPV is preferred because it induces intestinal immunity, is simple to administer, is well accepted by patients, results in immunization of some contacts of vaccinated persons, and has a record of having essentially eliminated disease associated with wild poliovirus in this country.[2] The choice of TOPV as the preferred poliovirus vaccine in the United States has also been made by the Committee on Infectious Diseases of the American Academy of Pediatrics and a special expert committee of the Institute of Medicine, National Academy of Science.[3,4] TOPV is also recommended for control of epidemic poliomyelitis.[2,3]

Past history of clinical poliomyelitis or prior vaccination with IPV in otherwise healthy individuals does not preclude the administration of TOPV when otherwise indicated.

Serologic evidence indicates that measles and rubella vaccines or combinations (measles-mumps-rubella vaccine) given simultaneously with trivalent oral poliovirus vaccine can be expected to give adequate antibody response.[5]

Routine poliomyelitis immunization for adults residing in the continental United States is not necessary because of extreme unlikelihood of exposure. However, primary immunization with IPV is recommended whenever feasible for those unimmunized adults subject to *increased risk* of exposure, as by travel to or contact

with epidemic or endemic areas and for those employed in hospitals, medical laboratories, clinics or sanitation facilities. If less than 4 weeks are available before protection is needed, a single dose of TOPV is recommended, with IPV given later if the person remains at increased risk. Immunization with IPV may be indicated for unimmunized parents and those in other special situations where, in the judgement of the attending physician, protection may be needed.[3] (see CONTRAINDICATIONS and ADVERSE REACTIONS.)

CONTRAINDICATIONS

Under no circumstances should this vaccine be administered parenterally

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

ORIMUNE *must not* be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia and agammaglobulinemia. It would also be prudent to withhold ORIMUNE from siblings of a child known to have an immunodeficiency syndrome. Further, ORIMUNE *must not* be administered to patients with altered immune states such as those occurring in thymic abnormalities, leukemia, lymphoma or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites or radiation. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least 6-8 weeks. IPV is preferred for immunizing all persons in this setting.[2,3,4,6,7]

PRECAUTIONS

Other viruses (including poliovirus and other enterovirus) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

It would seem prudent not to administer TOPV shortly after Immune Serum Globulin (ISG) unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If TOPV is given with or shortly after ISG, the dose probably should be repeated after three months, if immunization is still indicated.[8] However, ISG may not interfere with immunization with TOPV.[9]

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.

Use in Pregnancy

Although there is no convincing evidence documenting adverse effects of either TOPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, TOPV is recommended.[3] (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

ADVERSE REACTIONS

Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine, (see for example CONTRAINDICATIONS) and in persons who were in close contact with vaccinees.[2,3,4,10,11,12,13] The vaccine viruses are shed in the vaccinee's stools for at least 6 to 8 weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists.[2,10,14,15]

The risk of vaccine-associated paralysis is extremely small for vaccinees, susceptible family members and other close personal contacts.[2] However, prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian or other responsible person of the possibility of vaccine-associated paralysis. The Centers for Disease Control report that during the years 1969 through 1980 approximately 290 million doses of TOPV were distributed in the United States. In the same 12 years, 25 "vaccine-associated" and 55 "contact vaccine-associated" paralytic cases were reported. Twelve other "vaccine-associated" cases have been reported in persons (recipients or contacts) with immune deficiency conditions.[2] These statistics do not provide a satisfactory basis for estimating these risks on a per person basis.[14]

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be minimized by giving these adults three doses of IPV a month apart before the children receive ORIMUNE.[2] The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.[2]

The Immunization Practices Advisory Committee of the U.S. Public Health Service states:

"Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."[2]

The Immunization Practices Advisory Committee has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of Children."[2]

ADMINISTRATION

ORIMUNE is to be administered *orally, under the supervision of a physician. Under no circumstances should this vaccine be administered parenterally.* For convenience, the vaccine is supplied in a disposable pipette containing a single dose of 0.5 ml. The vaccine can be administered directly or mixed with distilled water, tap water free of chlorine, simple syrup USP or milk. Alternatively, it may be adsorbed on any one of a number of foods such as bread, cake or cube sugar.

Community Programs

Poliovirus Vaccine, Live, Oral Trivalent has been recommended for epidemic control. Within an epidemic area, TOPV should be provided for all persons over 6 weeks of age who have not been completely immunized or whose immunization status is unknown, with the exceptions noted under immunodeficiency.[2,3]

DOSAGE

Dose. Each single dose consists of 0.5 ml of Poliovirus Vaccine, Live, Oral Trivalent ORIMUNE.

Initial Administration (Primary Series)

Infants: The primary series is three doses. The Immunization Practices Advisory Committee (Public Health Service) recommends that the three dose immunization series be started at 6 to 12 weeks of age, commonly with the first DTP inoculation. The second dose should be given not less than 6 and preferably 8 weeks later. The third dose is an integral part of the primary immunization and should be administered 8 to 12 months after the second dose.[3]

The American Academy of Pediatrics recommends that the vaccine be administered at 2 months, 4 months, and at approximately 18 months of age. An optional dose of TOPV may be given at 6 months in areas where poliomyelitis is endemic.[3]

Administration to the newborn (under 6 weeks) is not generally recommended because of the varying persistence of maternal antibodies. However, in certain tropical endemic areas, where poliomyelitis has been increasing in recent years, the physician may wish to administer TOPV to the infant at birth, and complete the basic course during the first six months of life.[3] If the physician chooses to immunize the infant at birth, it may be wise to wait until the child is three days old, and it may be prudent to recommend abstention from breast-feeding for two to three hours before and after oral vaccination to permit establishment of the vaccine viruses in the gut.[16]

Older Children and Adolescents (through age 18): Two doses, given not less than 6 and preferably 8 weeks apart and the third dose 6 to 12 months after the second dose.[3]

Adults: See INDICATIONS and ADVERSE REACTIONS. Where ORIMUNE is given to unimmunized adults, the dosage is as indicated for children and adolescents.

Booster Doses - School Entrance: On entering elementary school, all children who have completed the primary series should be given a single follow-up dose of trivalent oral poliovirus vaccine.[2,3] All others should complete the primary series.

The Public Health Service Advisory Committee does not recommend routine booster doses of vaccine on the basis of current information, beyond that given at the time of entering school.[2] Recent data indicates that over 95% of children studied five years after full immunization with oral poliovirus vaccine had protective antibodies to all three types of poliovirus.[17]

Increased risk: If an individual who has completed a primary series is subjected to a substantially increased risk by virtue of contact, travel or occupation, a single dose of TOPV has been suggested.[2]

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MSD | M-M-R® II (MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE, MSD)

M-M-R® II
(Measles, Mumps, and Rubella Virus Vaccine Live, MSD)

DESCRIPTION

M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live, MSD) is a live virus vaccine for immunization against measles (rubeola), mumps and rubella (German measles).

M-M-R II is a sterile lyophilized preparation of (1) ATTENUVAX® (Measles Virus Vaccine Live, MSD), a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo, (2) MUMPSVAX® (Mumps Virus Vaccine Live, MSD), the Jeryl Lynn (B level) strain of mumps virus grown in cell cultures of chick embryo, and (3) MERUVAX® II (Rubella Virus Vaccine Live, MSD), the Wistar RA 27 3 strain of live attenuated rubella virus grown in human diploid cell (WI-38) culture.[1,2] The vaccine viruses are the same as those used in the manufacture of ATTENUVAX (Measles Virus Vaccine Live, MSD), MUMPSVAX (Mumps Virus Vaccine Live, MSD) and MERUVAX II (Rubella Virus Vaccine Live, MSD). The three viruses are mixed before being lyophilized. The product contains no preservative.

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 mL and contains not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of the U.S. Reference Measles Virus; 5,000 $TCID_{50}$ of the U.S. Reference Mumps Virus, and 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus. Each dose contains approximately 25 mcg of neomycin. The product contains no preservative. Sorbitol and hydrolyzed gelatin are added as stabilizers.

CLINICAL PHARMACOLOGY

Clinical studies of 279 triple seronegative children, 11 months to 7 years of age, demonstrated that M-M-R II is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced measles hemagglutination-inhibition (HI) antibodies in 95 percent, mumps neutralizing antibodies in 96 percent, and rubella HI antibodies in 99 percent of susceptible persons.

The RA 27 3 rubella strain in M-M-R II elicits higher immediate post-vaccination HI, complement-fixing and neutralizing antibody levels than other strains of rubella vaccine[3-9] and has been shown to induce a broader profile of circulating antibodies including anti-theta and anti-iota precipitating antibodies.[10,11] The RA 27 3 rubella strain immunologically simulates natural infection more closely than other rubella vaccine viruses.[11-13] The increased levels and broader profile of antibodies produced by RA 27 3 strain rubella virus vaccine appear to correlate with greater resistance to subclinical reinfection with the wild virus,[11,13-15] and provide greater confidence for lasting immunity.

Vaccine induced antibody levels following administration of M-M-R II have been shown to persist for at least two years without substantial decline.[16] Antibody levels after immunization with M-M-R (Measles, Mumps, and Rubella Virus Vaccine Live, MSD), containing the HPV-77 strain of rubella, have persisted for 10.5 years without substantial decline.[17] If the present pattern continues, it will provide a basis for the expectation that immunity following vaccination will be permanent. However, continued surveillance will be required to demonstrate this point.

INDICATIONS AND USAGE

M-M-R II is indicated for simultaneous immunization against measles, mumps, and rubella in persons 15 months of age or older. A booster is not needed.

Infants who are less than 15 months of age may fail to respond to the measles component of the vaccine due to presence in the circulation of residual measles antibody of maternal origin, the younger the infant, the lower the likelihood of seroconversion. In geographically isolated or other relatively inaccessible populations for whom immunization programs are logistically difficult, and in population groups in which natural measles infection may occur in a significant proportion of infants before 15 months of age, it may be desirable to give the vaccine to infants at an earlier age. Infants vaccinated under these conditions at less than 12 months of age should be revaccinated after reaching 15 months of age. There is some evidence to suggest that infants immunized at less than one year of age may not develop sustained antibody levels when later reimmunized. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization.[18]

reviously unimmunized children of susceptible pregnant women should ive live attenuated rubella vaccine, because an immunized child will be likely to acquire natural rubella and introduce the virus into the house-d.

Pregnant Adolescent and Adult Females

nmunization of susceptible non-pregnant adolescent and adult females hildbearing age with live attenuated rubella virus vaccine is indicated if tain precautions are observed (see below and PRECAUTIONS). Vaccinat susceptible postpubertal females confers individual protection against sequently acquiring rubella infection during pregnancy, which in turn vents infection of the fetus and consequent congenital rubella injury.[19] Women of childbearing age should be advised not to become pregnant for te months after vaccination and should be informed of the reasons for precaution.*

t is recommended that rubella susceptibility be determined by serologic ting prior to immunization.** If immune, as evidenced by a specific bella antibody titer of 1:8 or greater (hemagglutination-inhibition test), ccination is unnecessary. Congenital malformations do occur in up to ren percent of all live births.[20] Their chance appearance after vaccination uld lead to misinterpretation of the cause, particularly if the prior rubella-mune status of vaccinees is unknown.

Postpubertal females should be informed of the frequent occurrence of d-limited arthralgia and possible arthritis beginning 2 to 4 weeks after ccination (see ADVERSE REACTIONS).

ostpartum Women

t has been found convenient in many instances to vaccinate rubella-sceptible women in the immediate postpartum period. (See *Nursing others.*)

Revaccination: Children vaccinated when younger than 12 months of age ould be revaccinated. Based on available evidence, there is no reason to utinely revaccinate persons who were vaccinated originally when 12 onths of age or older. However, persons should be revaccinated if there is idence to suggest that initial immunization was ineffective.

ion with other Vaccines

Routine administration of DTP (diphtheria, tetanus, pertussis) and or OPV ral poliovirus vaccine) concomitantly with measles, mumps and rubella ccines is not recommended because there are insufficient data relating to e simultaneous administration of these antigens. However, the American cademy of Pediatrics has noted that in some circumstances, particularly hen the patient may not return, some practitioners prefer to administer all ese antigens on a single day. If done, separate sites and syringes should be sed for DTP and M-M-R □.[21]

M-M-R □ should not be given less than one month before or after administration of other virus vaccines.

CONTRAINDICATIONS

Do not give M-M-R □ to pregnant females; the possible effects of the acc ne on fetal development are unknown at this time. If vaccination of ostpubertal females is undertaken, pregnancy should be avoided for three onths following vaccination. (See PRECAUTIONS, *Pregnancy*.)

Anaphylactoid reaction to neomycin (each dose of reconstituted vaccine ontains approximately 25 mcg of neomycin).

History of anaphylactoid reaction to eggs (see HYPERSENSITIVITY TO GGS below).

Any febrile respiratory illness or other active febrile infection.

Active untreated tuberculosis.

Patients receiving immunosuppressive therapy. This contraindication oes not apply to patients who are receiving corticosteroids as replacement herapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic sys-ems.

Primary immunodeficiency states, including cellular immune deficien-ies, hypogammaglobulinemic and dysgammaglobulinemic states.

Individuals with a family history of congenital or hereditary immunodefi-iency, until the immune competence of the potential vaccine recipient is demonstrated.[22]

---

*NOTE: The Immunization Practices Advisory Committee (ACIP) has rec-ommended "In view of the importance of protecting this age group against rubella, reasonable precautions in a rubella immu-nization program include asking females if they are pregnant, excluding those who say they are, and explaining the theoretical risks to the others."[19]

**NOTE: The Immunization Practices Advisory Committee (ACIP) has stated "When practical, and when reliable laboratory services are available, potential vaccinees of childbearing age can have serologic tests to determine susceptibility to rubella. . . . However, routinely performing serologic tests for all females of childbear-ing age to determine susceptibility so that vaccine is given only to proven susceptibles is expensive and has been ineffective in some areas. Accordingly, the ACIP believes that rubella vaccina-tion of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing."[19]

7416509

M-M-R® □
(Measles, Mumps, and Rubella Virus Vaccine Live, MSD)

HYPERSENSITIVITY TO EGGS

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic or other immedi-ate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion should not be vaccinated. Evidence indicates that persons are not at increased risk if they have egg allergies that are not anaphylactic in nature. Such persons may be vaccinated in the usual manner. There is no evidence to indicate that persons with allergies to chickens or feathers are at increased risk of reac-tion to the vaccine.[19]

PRECAUTIONS

General

Adequate treatment provisions including epinephrine, should be avail-able for immediate use should an anaphylactoid reaction occur.

Due caution should be employed in administration of M-M-R □ to persons with a history of febrile convulsions, cerebral injury or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur following vaccination. (See ADVERSE REACTIONS.)

Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of human immune serum globulin.

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7-28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.[19] However, transmission of the rubella vaccine virus to infants via breast milk has been documented (see *Nursing Mothers*).

There are no reports of transmission of live attenuated measles or mumps viruses from vaccinees to susceptible contacts.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either before or simultaneously with M-M-R □.

As for any vaccine, vaccination with M-M-R □ may not result in seroconversion in 100% of susceptible persons given the vaccine.

Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with M-M-R □. It is also not known whether M-M-R □ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination (see CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) In a 10 year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after con-ception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syn-drome;[23] (2) Although mumps virus is capable of infecting the placenta and fetus, there is no good evidence that it causes congenital malformations in humans. Mumps vaccine virus also has been shown to infect the placenta, but the virus has not been isolated from the fetal tissues from susceptible women who were vaccinated and underwent elective abortions;[24] and (3) Reports have indicated that contracting of natural measles during preg-nancy enhances fetal risk. Increased rates of spontaneous abortion, still-birth, congenital defects and prematurity have been observed subsequent to natural measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects.

Nursing Mothers

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating postpartum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants.[25] In the infants with serological evidence of rubella infection, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella.[26,27] Caution should be exercised when M-M-R □ is administered to a nursing woman.

ADVERSE REACTIONS

Because of the slightly acidic pH (6.2-6.6) of the vaccine, patients may complain of burning and or stinging of short duration at the injection site.

The adverse clinical reactions associated with the use of M-M-R II are those expected to follow administration of the monovalent vaccines given separately. These may include malaise, sore throat, headache, fever and rash; mild local reactions such as erythema, induration, tenderness and regional lymphadenopathy, parotitis, orchitis; nerve deafness; thrombocy-topenia and purpura; allergic reactions such as wheal and flare at the injection site or urticaria; and arthritis, arthralgia and polyneuritis.

syringe to be used for reconstitution. Inject all the ...luent in the syrir into the vial of lyophilized vaccine, and agitate to mix thoroughly. Wi draw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

10 Dose Vial (available only to government agencies/institutions)

Withdraw the entire contents (7 mL) of the diluent vial into the sterile syringe to be used for reconstitution, and introduce into the 10 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. The outer labeling suggests "For Jet Injector or Syringe Use". Use with separate sterile syringes is permitted for containers of 10 doses or less. The vaccine and diluent do not contain preservatives; therefore, the user must recognize the potential contamination hazards and exercise special precautions to protect the sterility and potency of the product. The use of aseptic techniques and proper storage prior to and after restoration of the vaccine and subsequent withdrawal of the individual doses is essential. Use 0.5 mL of the reconstituted vaccine for subcutaneous injection.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

Each dose contains not less than the equivalent of 1,000 $TCID_{50}$ of the U.S. Reference Measles Virus, 5,000 $TCID_{50}$ of the U.S. Reference Mumps Virus and 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. M-M-R II, when reconstituted, is clear yellow.

HOW SUPPLIED

No. 4749 — M-M-R II is supplied as a single-dose vial of lyophilized vaccine, NDC 0006-4749-00, and a vial of diluent.

No. 4681/4309 — M-M-R II is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A), NDC 0006-4681-00; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature.

Available only to government agencies/institutions:

No. 4682X — M-M-R II is supplied as one 10 dose vial of lyophilized vaccine.

NDC 0006-4682-00, and one 7 mL vial of diluent.

Storage

It is recommended that the vaccine be used as soon as possible after reconstitution. Protect vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2 - 8°C (35.6 - 46.4°F) and discard if not used within 8 hours.

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REPORT OF ADVERSE EVENT FOLLOWING IMMUNIZATION
DEPARTMENT OF HEALTH & HUMAN SERVICES, PUBLIC HEALTH SERVICE, Centers for Disease Control, Atlanta, Georgia 30333

PATIENT ID

Immunization Project Area _____ | State Code ☐☐ | Seq. No. ☐☐☐☐ | County Where Administered: _____ County Code ☐☐☐ | MSAEFI REPORT NO. FOR CDC USE ONLY

Date of Birth ☐☐ Mo. ☐☐ Day ☐☐ Yr. | Sex M ☐ F ☐ | Date of Initial Report ☐☐ Mo. ☐☐ Day ☐☐ Yr. | Source of Information MD/DO ☐ Nurse ☐ Family ☐ Other ☐ _____

VACCINE HISTORY

Date of Immunization ☐☐ Mo. ☐☐ Day ☐☐ Yr.

Vaccine Administered By: Pub. ☐ Pvt. ☐ Mil. ☐ Other ☐

Vaccine Purchased By: Pub. ☐ Pvt. ☐ Mil. ☐ Other ☐

Enter Below All Vaccines Given on the Date of Immunization:

	Vaccine Type	Mfgr.	Lot Number	Route	Site	No. Prior Doses
A						
B						
C						
D						

CLINICAL DESCRIPTION OF PRESENT ILLNESS

SIGNS AND SYMPTOMS OF PRESENT ILLNESS

Onset of 1st Sign or Symptom: ☐☐ Mo. ☐☐ Day ☐☐ Yr.

	Yes	No	Unk
1. Fever: Temp ≥(100°F (37.8°C) (7806)	☐	☐	☐
Felt Hot, But Temperature Not Measured: (7800)	☐		
Highest Measured Temperature ☐☐☐.☐ F/C			
2. Local Reaction: Site _____			
Pain, Swelling, Increased Warmth, Induration or Lump Without Abscess (9993)	☐	☐	☐
Abscess Formation — Required Drainage or Drained Spontaneously (6829)+(9993)	☐	☐	☐
Results of Culture _____			
3. Rash: Other Than at Injection Site (7821)	☐	☐	☐
4. Adenopathy:			
Local (Injection Site Area) (7856)	☐	☐	☐
Generalized (7856)	☐	☐	☐
5. Allergic Event: (9995)	☐	☐	☐
Hives (7080)	☐	☐	☐
Angioneurotic Edema (9951)	☐	☐	☐
Wheezing/Asthma (4939)	☐	☐	☐
Anaphylaxis (9994)	☐	☐	☐
If "Yes," Interval from Vaccination to Onset: < 30 min ☐ 30 min-6 hrs ☐ > 6 hrs ☐			
Was Blood Pressure Measured?	☐	☐	☐
If "Yes," Lowest B.P. ☐☐☐/☐☐☐			
6. Arthralgia/Arthritis:			
Pain in Joints (7194)	☐	☐	☐
Inflammation of Joints (Redness, Swelling, Tenderness) (7109)	☐	☐	☐
7. Convulsions: (7803)	☐	☐	☐
If "Yes," How many Episodes Following Immunization ☐☐			
8. Encephalitis and/or Encephalopathy: (3483)	☐	☐	☐
Abnormal Lumbar Puncture (Enter Results in Laboratory subsection) (7920)	☐	☐	☐
Signs of Increased Intracranial Pressure (3481)	☐	☐	☐
Focal Neurologic Signs (3409)	☐	☐	☐
Coma or Marked Alteration in Level of Consciousness (7800)	☐	☐	☐

	Yes	No	Unk
9. Guillain–Barré Syndrome: (3570)	☐	☐	☐
10. Reye's Syndrome: (3318)	☐	☐	☐
11. Polio: (0469)	☐	☐	☐
12. Paralysis other than GBS, Reye's Syndrome or Polio (3449)	☐	☐	☐
13. Other Neurologic Symptoms and Diagnoses:			
Aseptic Meningitis (3479)	☐	☐	☐
Infantile Spasms (Hypsarrhythmia, drop seizures) (3456)	☐	☐	☐
Bell's Palsy (3510)	☐	☐	☐
Hearing Loss (3899)	☐	☐	☐
Neuritis, Neuralgia (7292	☐	☐	☐
Paresthesias (7820)	☐	☐	☐
Screaming Episode (High-Pitched Abnormal Cry or Screaming Lasting ≥ 3 Hours) (7998)	☐	☐	☐
Neurologic Symptoms not cited above (specify) _____	☐	☐	☐
14. Miscellaneous:			
Hypotonic, Hyporesponsive Episode (7859)	☐	☐	☐
Idiopathic Thrombocytopenic Purpura	☐	☐	☐
If "Yes," Lowest Platelet count (2873) ☐☐☐☐☐			
Pancreatitis (5770)	☐	☐	☐
Parotitis (5272)	☐	☐	☐
15. Death:			
Sudden Infant Death Syndrome (SIDS) (7980)	☐	☐	☐
Non-SIDS Death (7981)	☐	☐	☐
If "Yes," Cause(s): _____			

LABORATORY:

	Performed Yes	No	Unk	Results Normal	Abnormal
EEG	☐	☐	☐	☐	☐ (7940)
BRAIN SCAN	☐	☐	☐	☐	☐ (7940)
LUMBAR PUNCTURE	☐	☐	☐	☐	☐ (7920)

Results if Abnormal:
WBC's _____ Opening Pressure _____
Lymphs (%) _____ Culture Results _____
Glucose _____ Other _____
Total Protein _____

Other Pertinent Information: _____

Signature of MSAEFI Coordinator: _____

Seen by Health Care Provider: ☐ Yes ☐ No ☐ Unk ☐ Number of Visits | Hospitalized ☐ Yes ☐ No ☐ Unk ☐☐ Number of Days

PAST HISTORY

Previous Illness Following Immunization: Yes ☐ No ☐ If "Yes," Date: ☐☐ Mo. ☐☐ Day ☐☐ Yr.
Vaccine _____
Describe Illness _____

Previous Convulsions in Patient: Yes ☐ No ☐ Unk ☐
If "Yes," ☐ With Fever ☐ Without Fever

History of Convulsions in Siblings or Parents: Yes ☐ No ☐ Unk ☐
If "Yes," ☐ With Fever ☐ Without Fever

FOLLOWUP

SEVEN DAY FOLLOWUP: If recovered, send to State Office — ☐☐ Mo. ☐☐ Day ☐☐ Yr.

30 DAY FOLLOWUP: If not recovered at 7 days, carry out 30 Day Followup and send to State Office — ☐☐ Mo. ☐☐ Day ☐☐ Yr.

	Duration of Illness	Recovered	Partially Recovered*	Not Recovered*	Not Located	Dead
SEVEN DAY FOLLOWUP	Days ☐☐	☐	☐	☐	☐	☐
30 DAY FOLLOWUP	Days ☐☐	☐	☐	☐	☐	☐

*Comments _____

Reviewed By Immunization Project Physician (Items 7 - 15 and Anaphylaxis): ☐ Yes ☐ No ☐ Unk
Signature of Reviewing M.D. _____

CDC USE

Results of One-Year Followup: Recovered ☐ Partially Recovered* ☐ Not Recovered* ☐ Dead ☐ Not Located ☐ *Comments _____

This rep[illegible] law (42 USC 247b; 42 CFR 51 b). Its submission is needed to monitor possible reactions to vaccination and [illegible] volume[illegible] ed as a condition of immunization grant awards.

CDC 71.19

LECTURE 8

IMMUNIZATIONS

A Dissenting View

Richard Moskowitz, M.D.

INTRODUCTION OF THE SPEAKER

Lori Andrews: Thank you. Next, we'll be hearing from Dr. Richard Moskowitz, who will talk to us about immunizations. Dr. Moskowitz graduated Phi Beta Kappa from Harvard University and received his medical degree at New York University, but he has not taken a narrow-minded approach to his professional interest. From 1963 to 1965 he was a graduate fellow in the department of philosophy at the University of Colorado graduate school. He studied homeopathy in Athens, Greece, as well as at the National Center for Homeopathy in Washington, D.C., where he currently serves as the director of publications and is a member of the permanent teaching faculty. He has also practiced in a variety of settings. He was the founder and medical director of the Boulder Free Clinic and a volunteer physician on the Medical Committee for Human Rights in New York. He's now in the private practice of classical homeopathy and has published extensively in journals such as *Homeopathy Today*, *Homeotherapy*, and *The Journal of the American Institute of Homeopathy*. Thank you, Dr. Moskowitz.

LECTURE

Dr. Moskowitz: For the past 10 years or so, I have felt a deep and growing compunction against giving routine immunizations to children. It began with the fundamental belief that people have the right to make that choice for themselves. Soon I discovered that I could no longer bring myself to give the injections even when the parents wished me to.

At bottom, I have always felt that the attempt to eradicate entire microbial species from the biosphere must inevitably upset the balance of nature in fundamental ways that we can as yet scarcely imagine. Such concerns loom ever larger as new vaccines continue to be developed, seemingly for no better reason than that we have the technical capacity to make them and thereby to demonstrate our power, as a civilization, to manipulate the evolutionary process itself.

Purely from the viewpoint of our own species, even if we could be sure that the vaccines were harmless, the fact remains that they are compulsory, that all children are required to undergo them without any sensitive regard for basic differences in individual susceptibility, to say nothing of the wishes of the parents or the children themselves.

Most people can readily accept the fact that, from time to time, certain laws that some of us strongly disagree with may be necessary for the public good. But the issue in this case involves nothing less than the introduction of foreign proteins or even live viruses into the bloodstream of entire populations. For that reason alone, the public is surely entitled to convincing proof, beyond any reasonable doubt, that artificial immunization is in fact a safe and effective procedure, in no way injurious to health, and that the threat of the corresponding natural diseases remains sufficiently clear and urgent to warrant mass inoculation of everyone, even against their will if necessary.

Unfortunately, such proof has never been given; and, even if it could be, continuing to employ vaccines against diseases that are no longer prevalent or no longer dangerous hardly qualifies as an emergency.

Finally, even if such an emergency did exist, and artificial immunization could be shown to be an appropriate response to it, the decision would remain essentially a *political* one, involving issues of public health and safety that are far too important to be settled by any purely scientific or technical criteria, or indeed by *any* criteria less authoritative than the clearly articulated sense of the community about to be subjected to it.

For all of these reasons, I want to present the case against routine

immunization as clearly and forcefully as I can. What I have to say is not quite a formal theory capable of rigorous proof or disproof. It is simply an attempt to explain my own experience, a nexus of interrelated facts, observations, reflections and hypotheses which, taken together, are more or less coherent and plausible and make intuitive sense to me.

I offer them to the public in part because the growing refusal of parents to vaccinate their children is so seldom articulated or taken seriously. The fact is that we have been taught to accept vaccination as a sort of involuntary communion, a sacrament of our own participation in the unrestricted growth of scientific and industrial technology, utterly heedless of the long-term consequences to the health of our own species, let alone to the balance of nature as a whole. For that reason alone, the other side of the case urgently needs to be heard.

1. Are the Vaccines Effective?

There is widespread agreement that the time period since the common vaccines were introduced has seen a remarkable decline in the incidence and severity of the corresponding natural infections. But the customary assumption that the decline is *attributable* to the vaccines remains unproven, and continues to be seriously questioned by eminent authorities in the field. The incidence and severity of whooping cough, for example, had already begun to decline precipitously long before the pertussis vaccine was introduced,[1] a fact which led the epidemiologist C. C. Dauer to remark, as far back as 1943:

> If mortality (from pertussis) continues to decline at the same rate during the next 15 years, it will be extremely difficult to show statistically that (pertussis immunization) had any effect in reducing mortality from whooping cough.[2]

Much the same is true not only of diphtheria and tetanus, but also of TB, cholera, typhoid, and other common scourges of a bygone era, which began to disappear toward the end of the nineteenth century, perhaps partly in response to improvements in public health and sanitation, but in any case long before antibiotics, vaccines, or any specific medical measures designed to eradicate them.[3]

Reflections such as these led the great microbiologist René Dubos to observe that microbial diseases have their own natural history, indepen-