Volume 3 - Issue 2

PKIDs' News

"You must do the thing you think you cannot do."

Eleanor Roosevelt

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VACCINE RESEARCH AND DEVELOPMENT:

TURNING SCIENCE INTO NEW TOOLS FOR PREVENTION AND TREATMENT

by Bruce Gellin, MD, MPH, and Rosalind H. Lin.

[Ed. note: We have so many questions about childhood immunizations come our way, we decided it would be helpful to devote an entire newsletter to the topic. Dr. Gellin, Dr. Kohl, Dr. Humiston and Ms. Lin have helped out with wonderful articles about vaccine issues - past, present and future - and we've included an immunization schedule for your personal use. We hope you find this information useful. We will return to our regular format in the fall issue.]

There is no better example of the expression, "An ounce of prevention is worth a pound of cure," than modern immunizations. Vaccines are one of the greatest achievements in medicine and the record of progress will continue as a result of ongoing research. No other public health practice has had such a dramatic effect on the control of disease. (See page 7.)

Not only do vaccines protect people from the acute phase of serious infectious diseases, but they also prevent the disabilities and death that many of these diseases cause. Without immunization, millions of children and adults would contract serious diseases that are now prevented with vaccines. In fact, it is estimated that 25 of the additional 30 years of life expectancy that have been added since 1900 are attributed to public health interventions, with vaccines at the top of that list.

Vaccine research and development has come a long way since the days of the earliest vaccines. Developments in immunology, the biotechnology revolution, and most recently genomics are all likely to provide new opportunities to develop vaccines against a wide range of diseases. Improved understanding of the molecular basis of many infectious diseases and the mechanisms of immune protection will allow for the development of vaccines that are designed with these features in mind and minimize much of the empiricism that created vaccines of yesterday and today.

When people think of immunizations, they often picture black and white photos from yesteryear depicting the ravages of epidemics of infectious diseases. However, because they affect the immune system, not only do vaccines offer the possibility to prevent a number of infectious diseases for which there are not currently vaccines, but they may also prevent or 'treat' a number of other diseases including diabetes, cancer and allergies.

While many of the diseases that new vaccines will target are in the developed world, a new commitment inspired by the Bill and Melinda Gates Foundation (http://www.gatesfoundation.org)

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"Mountains cannot be surmounted except by winding paths."

Johann Wolfgang Von Goethe

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and the Global Alliance for Vaccines and Immunizations (http://www.vaccinealliance.org) should also stimulate the development of vaccines for diseases that afflict millions of children and adults around the world: malaria, hookworm, tuberculosis and HIV. Finally, the new era of vaccine development is greatly assisted by research that informs new ways of controlling the immune system to prevent and/or treat a wide range of diseases.

Another result of the improved understanding of immunology is the potential to create an array of new vaccine technologies. Perhaps one day we will look back at the shots we give today in the same way that we view the tall ships that were once the heart of international travel and commerce. Given the rapidly accelerating advances, the immunization program's 'tool kit' is going to look quite different in the future. For example, our expanding understanding of mucosal immunity is likely to lead to a new generation of mucosal vaccines that can be given orally, as an intranasal aerosol, or applied directly to the surface of the skin in much the same way that we apply nail polish.

There has been a steady progression of vaccine development that has led to an expanding list of licensed vaccines. While this represents our ability to prevent the diseases that were once referred to as the "usual childhood infections," the addition of these vaccines has also made the recommended childhood immunization schedule increasingly complex. But the reality is that in barely over a decade, the licensure and introduction of several vaccines has further improved infant and child health (see comparative recommended schedules insert and page 11).

As this newsletter went to press, the Advisory Committee on Immunization Practices (ACIP/CDC), was considering recommendations for the recently licensed pneumococcal conjugate vaccine - a vaccine that will further reduce the mortality and morbidity caused by a bacterium (*Streptococcus pneumoniae*). This is now the leading cause of bacterial meningitis in early childhood, a distinction previously held by *Haemophilus influenzae* type b (Hib) before the near elimination of invasive Hib diseases (meningitis, pneumonia, bacteremia) following the introduction of a similar vaccine just a decade ago.

The many new vaccines have led some parents to express concern that immunizations may be overwhelming their children's immune systems. Except for those who live in bubbles, we are continually exposed to bacteria, viruses, allergens and foreign proteins as part of daily living. The immune system can handle hundreds of thousands, if not millions of such challenges. For example, depending on the particular virus, we may be exposed to up to 10 foreign proteins during a single episode of an upper respiratory infection. A routine strep throat will present between 25 and 50 foreign proteins to the immune system. Since modern vaccines are made of refined components of the organism, they actually present less of a challenge to the immune system than an infection would. The reason that immunizations are given to infants at such a young age is to protect them from the diseases that are much more severe when they are contracted early in life.

Combination vaccines: Reducing shots without reducing effectiveness

Vaccines that are able to prevent several infections simultaneously, the so-called combination vaccines, are not new concepts. Many vaccines that have been given for decades have combined the disease-preventing potential of individual vaccines. For example, the DTaP vaccine combines vaccines that prevent diphtheria, tetanus and pertussis (whooping cough). The MMR vaccine (measles, mumps and rubella vaccine) is a single vaccine that prevents these three viral illnesses. Perhaps less obvious is the influenza vaccine that is reconstructed annually and contains inactivated forms of the three influenza viruses that are most likely to cause the season's infection. And most are unaware that the polio vaccine (both the older OPV [oral polio vaccine] and the currently recommended IPV [inactivated polio vaccine]) are made from the three polio viruses that cause the disease.

It is hoped that developments in new combination vaccines that combine the effectiveness and safety of individual vaccines into one will simplify the process of routine childhood immunization.

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Should the current schedule become much more complex, some parents may feel that they need to make difficult choices about which vaccines they might want to defer. If the number of vaccines on a given visit becomes a barrier to full immunization then the investments made to develop vaccines that prevent these serious infectious may be lost. Even the best product will have no effect if it remains on the shelf.

It is for this reason that the creation of new combination vaccines are seen by physicians, nurses, parents and patients as one of the most important developments in the vaccine development arena. But because some vaccines may interfere with the immune response to another vaccine when administered together, developing new combination vaccines is not as simple as blending paint to achieve the color you desire. To assure that a combination vaccine is both as safe and effective as its individual components, it requires the same long and meticulous series of clinical studies needs that are performed on any new vaccine.

The research and development pipeline: What's new? What should we expect in the near future?

Research conducted and supported by the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), academic medical centers, research foundations, biotechnology companies and multinational vaccine companies is creating a new set of vaccines that may some day be available. Before a vaccine is considered for licensure by the FDA it is evaluated in a number of ways. This process could take up to ten years (and sometimes longer) but is designed to assure that vaccines receive every level of scrutiny at each stage. This evaluation process is designed to insure that the vaccines do what they are intended to do without untoward effects. When animal (pre-clinical) studies indicate that a vaccine candidate has promise as a human vaccine, it will then undergo three phases of clinical trials in human beings before the data is presented to the FDA advisory committees for their review.

To establish a basic understanding of safety and immune response in humans, Phase 1 trials are small, involving only a few dozen volunteers. To continue to gather information on efficacy and safety, more extensive Phase 2 clinical trials are conducted, often with several hundred volunteers. It is in these studies that the optimal dose size, number of doses that should be administered and the interval between doses (the "schedule") is determined. Only vaccine candidates that pass these tests are entered into much larger Phase 3 clinical trials. These trials may have several thousand participants and often take several years to complete.

Because these studies are performed to determine whether the vaccine will prevent a disease in the population, a large study population is needed. In addition, because they are evaluating the vaccine's effectiveness, once immunized, study participants are followed for several years to compare the rates of disease (e.g., pneumococcal meningitis) in the group that received the vaccine compared with another group (control group) that did not receive the vaccine, but was at the same risk of contracting the infection. For example, the definitive Phase 3 clinical study of the pneumococcal conjugate vaccine required 37,000 volunteers. [Of note, perhaps the largest clinical vaccine trial ever conducted was the original inactivated polio vaccine (Salk vaccine). Initiated in the early 1950s, it included over a million children around the country.]

All of the information generated by these trials as well as details about each step of the manufacturing process is submitted for review by an expert FDA advisory committee for consideration of a license. Currently, there are 55 vaccines licensed by the FDA (www.fda.gov). To get a glimpse of the many vaccines in the pipeline, the National Institute of Allergy and Infectious Disease's *Jordan Report 2000* will provide the clearest snapshot of the many vaccines that are currently in development (http://www.niaid.nih.gov/publications/jordan). Because there are currently hundreds of vaccines that are in the various stages of research and development, there isn't space to cover them all. But a few selected examples (below) will give a sense of what can be expected.

What's new? What's coming?
Lyme vaccine

Lyme disease is caused by a bacterium named *Borrelia burdorferi* that is carried by a tick. In 1998, 14,646 cases were reported to the CDC, which was a 19 percent increase from the year before. In 1998, the FDA licensed a Lyme vaccine for individuals between the ages of 15 and 70. This vaccine was 80 percent effective at preventing Lyme disease. Currently, studies are examining efficacy of the Lyme vaccine in children under 15 years of age.

Maternal immunization against Group B Strep: Protecting babies from day one.

Group B strep (GBS) is the leading cause of death and infection from bacteria in newborn infants, as well as peripartum women. It is also an important pathogen in older adults and those with a number of chronic medical conditions. Since there are at least five different subtypes of GBS, an effective vaccine will require protection against each of the different bacteria.

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At the present time, vaccines for each of the 5 subtypes have been prepared and are being evaluated before being combined into a multicomponent combination vaccine. Another challenge to the development of this vaccine is the disease itself. Because this severe infection affects newborns in their first days of life, in order for a vaccine to be effective in preventing this disease, it will have to be 'working' soon after birth. Because the immune response to any vaccine may take a week or longer, one approach to preventing GBS disease is to administer the vaccine to women of childbearing age or during pregnancy so that the mother's immune system will be generating the antibodies that will be passed to the baby. This approach takes advantage of the naturally occurring maternal antibodies that all babies receive from their mother.

Hepatitis C and the vaccine

The hepatitis C virus (HCV) is a blood-borne infection that causes 12 percent of the acute viral hepatitis in the United States. 35,000 cases occur annually, with 85 percent of those infected becoming chronic carriers at a total yearly cost of $600 million (excluding transplants). Most carriers are asymptomatic. Most cases of HCV infection occur among young adults (especially injecting drug users), and sexual transmission may account for as many as 20 percent of cases. Each year, there are 8,000 to 10,000 deaths and approximately 1,000 liver transplants performed in the U.S. as a result of HCV infection. The development of an effective vaccine is hindered by the genetic and antigenic diversity of the virus. Early vaccine studies in chimpanzees have shown limited protection, so it is clear that an effective vaccine for humans is still work in progress.

The quest for a CMV (cytomegalovirus) vaccine

Approximately 50 percent of the U.S. population have been infected with cytomegalovirus (CMV). In healthy individuals, CMV infection may result in an asymptomatic or mononucleosis-like illness. However, in patients with impaired immune systems, CMV infection may be a serious and even life-threatening problem. Given the burden of this disease - 37,000-40,000 infants are born in the U.S. with congenital CMV each year and 10,000 develop profound progressive deafness and/or mental retardation from infection - the importance of development of CMV vaccine is undeniable. Several vaccines for CMV are currently in Phase 1 and Phase 2 clinical trials. The vaccines have been well tolerated, and stimulate high level of antibodies, which should correlate with protection against disease. However, formal Phase 3 studies of effectiveness are needed.

A Vaccine against Diabetes?

Type I diabetes (childhood-onset or juvenile diabetes) affects more than 13,000 children and young adults in the United States each year. While the cause of diabetes is unknown, the disease process results from the immune system's destruction of the insulin-producing cells in the pancreas. A vaccine that can prevent diabetes would obviously provide many health and economic benefits. Currently, successful prevention of diabetes has been shown in animal models by administration of pancreatic antigens. Individual pancreatic antigens such as insulin or their peptide fragments can be used to limit the immune system's attack on insulin-producing cells. A vaccine that will prevent diabetes is still a long way off, but research is underway.

Vaccines against cancer

When a virus is the cause of cancer, preventing the viral infection will prevent cancer from starting. The hepatitis B vaccine is actually the world's first cancer vaccine. By preventing the infection that causes liver cancer, it prevents the problem from beginning. The impact of hepatitis B vaccination has been amply demonstrated in a nationwide hepatitis B vaccination program implemented in Taiwan in July 1984. As a result, the hepatitis B carrier rate decreased from 10 to less than 2 percent, and hepatocellular carcinoma in children has cut in half within 15 years. Similar success has been demonstrated in long-term studies of Native American populations where a high rate of chronic hepatitis B virus infection led to high rates of liver cancer. Since it is now known that some strains of the human papillomavirus (HPV) are the cause of cervical cancer, and a vaccine that prevents HPV has been developed and is currently being evaluated, it is likely to be the world's next true anti-cancer vaccine.

Melanoma and renal cell cancer

The incidence of melanoma is doubling every 6 to 10 years. Many clinical trials are underway to induce a specific anti-tumor response to a vaccine. In this case the vaccine is more of a therapeutic than a preventive tool, but like other vaccines, its effect is on the immune system. For example, a recombinant vaccine that helps to stimulate T-cells within the melanoma is currently in Phase 1 trials. Also, a Phase 2 study is being done with a recombinant vaccine that stimulates the immune system by a substance called interleukin 2 (IL-2), a powerful chemical modulator of the immune response which may help to limit tumor growth and shrink some melanomas.

Renal cell carcinoma is another cancer for which vaccines are being developed. Similar methods of preventing cancer by stimulating the immune system, with T-cells or IL-2, are currently being studied in animal models.

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The use of "autologous" vaccines, where a piece of the tumor removed from a patient is used to make a vaccine for that patient, is currently being evaluated. A Phase 2 trial has been completed involving an autologous vaccine and another chemical (interferon) that regulates the immune response. Initial results demonstrate an impact on the immune system, however, the clinical effect was disappointing and none of the patients in this small study had any detectable improvement on their tumor. Additional studies of alternative approaches to autologous vaccines are currently in progress.

Shots: a thing of the past?

Alternative ways of delivering vaccination are also important in the development of new vaccines. Transcutaneous administration, or administration of vaccine to the skin, is a new method that may become practical. Phase 1 trials have shown that immune response could be activated in 15 minutes, so a skin patch might only need to be worn briefly.

Nasal immunization has been developed, especially in the realm of the influenza vaccines. Influenza vaccines administered by nasal spray are being used in Russia, and have been under development in the U.S. since the 1960s. The advantage of this type of vaccine is ease of administration. In a recent study, it was shown to be 86 percent effective at preventing influenza.

Maternal immunization may offer the best approach to immune protection for the newborn. This approach is currently the basis of the World Health Organization's neonatal tetanus immunization program. In addition to its application to preventing Group B strep infection, this approach may also be useful in preventing respiratory synctial virus (RSV) infection, a leading cause of hospitalization in young infants.

A Global Village, A Global Vaccine Challenge

In the next 10 years, vaccines for HIV/AIDS, malaria and tuberculosis will be developed. On March 2, 2000, Clinton met with leaders of the world's vaccine companies, foundations and international organizations to announce new partnerships to develop and deliver these vaccines. The commitment to the development of these novel partnerships in meeting the scientific challenges to create vaccines for these global threats is likely to inspire a series of discussions and meetings in the coming months and years. Whether the energy created by these sessions translates into effective vaccines that can be made available to those most in need is less predictable.

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"It is difficult to say what is impossible, for the dream of yesterday is the hope of today and the reality of tomorrow."

Robert H. Goddard

"An idealist believes the short run doesn't count.

"A cynic believes the long run doesn't matter.

"A realist believes that what is done or left undone in the short run detemines the long run."

Sidney J. Harris

A Brief, Selected and at Times, Personal History of Immunization

by Steve Kohl, MD

The history of immunization of humans, and also animals, fills many textbooks. We shall begin with a very selected history of some highpoints of immunization.

Smallpox

Most of us thankfully have never seen a case of smallpox, and in fact, most of us have not even been immunized against smallpox. In the past centuries smallpox was a dreaded cause of death and disfigurement. Survivors carried the scars, or pox marks, for the rest of their lives. In the 18th century in the U.S., epidemics involved as much as one-third of the populations. Smallpox is believed to have killed more people than all other infectious diseases combined!!

The ancient Chinese used smallpox fluid from mild human cases to immunize, a practice that spread to Europe in the 1700s. While often protective, severe cases of smallpox could result from this type of immunization.

In the late 1700s Dr. Edward Jenner, an English country physician, was told by a dairy maid that, since she had cowpox, a mild disease passed from cows to humans, she could not get smallpox. Dr. Jenner infected a child with cowpox from a milkmaid. When he boldly challenged the child with the smallpox virus the child was protected. Thus the first "modern vaccine" was created in 1796.

Smallpox remained a problem until widespread immunization with the cowpox vaccine. The cowpox disease was called vaccinia, hence the name vaccination. In 1966 the World Health Organization began a campaign to eliminate smallpox by organizing a worldwide immunization program. Even with the difficulty of administering the vaccine, in 1977 the last case of smallpox occurred in Somalia, Africa. For the first time humans had been able to eliminate an infectious disease by routine immunization.

The smallpox virus still exists in two heavily guarded freezers in the U.S. and Russia. Scientists are debating whether to destroy the virus or to continue to use it in research.

Polio

Polio is another infectious disease that is not seen now in the U.S. Many of us "older" folks can remember when it was unsafe to swim in public pools or drink from water fountains when the summer epidemics swept across the country. In the 1950s, 20,000 cases of paralytic polio occurred each year.

With the isolation of the 3 polio viruses in the late l940s, Dr. Jonas Salk was able to grow the viruses and then inactivate or kill them to create the first successful vaccine against polio. In 1954 I was one of several million school children who participated in a huge trial of the vaccine, compared with a series of placebo, or fake, injections. The trial was funded by the March of Dimes, an organization founded with the help of President Franklin Roosevelt, a polio survivor.

When the code to the year-long study was broken, I was found to have received the real vaccine, while my two cousins received the placebo. More importantly, the vaccine was about 85 percent protective against paralytic polio! By the worldwide use of oral polio vaccine, introduced by Dr. Sabin in the 1960s, we have eliminated polio in the U.S. The last case of wild polio disease was in 1979!

It is hoped that in the next two years polio will join the list, with smallpox, as a disease eradicated by a successful worldwide vaccination program. Until the polio virus is gone from the world it will be necessary for us living in the U.S. to continue polio immunization to protect ourselves from imported cases of polio. The return to using the killed, injectable vaccine makes for a safer immunization for all of our children.

Haemophilus Influenzae (H flu) Disease

A few short years ago H. flu was the major cause of bacterial meningitis, a deadly brain infection. About 20,000 children a year in the U.S. were infected with H. flu.

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Vaccine Prevention of Childhood Diseases

Disease	Vaccine	Recorded Cases in US/Yr Before Vaccine	Percent Reduction With Vaccine
Diphtheria	DPT*	206,000	100%
Pertussis	DPT*	265,000	98%
Tetanus	DPT*	1500	98%
Polio	Polio	21,000	100%
Measles	MMR**	894,000	99.9%
Mumps	MMR**	152,000	99.5%
Rubella	MMR**	57,600	99.8%
H. flu	H. flu	20,000	98%

*DPT--Diphtheria, Pertussis, Tetanus vaccine
**MMR-Measles, Mumps, Rubella vaccine

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About 5 percent died and one-third of the survivors had brain damage, including: paralysis, hearing problems and learning disorders. The first H. flu vaccines introduced in the 1980s were protective for older children, but not younger children, which was a big problem since most H. flu disease occurred in young children. With scientific advances it was found that if the original vaccine (a part of the bacteria coat) was hooked to a protein, then young children's immune systems could recognize it and make antibodies to protect the child. Introduced in the 1990s, these new vaccines have had widespread acceptance and have resulted in a 95 percent or more decrease in H. flu disease in the U.S.

Protection by Vaccines

It would be too tedious for me, the writer, and you, the reader, to read the story of all the current childhood vaccines. Instead the table above lists the standard childhood vaccines and their success in prevention of serious childhood diseases.

There are a number of new vaccines recently added to the childhood vaccine schedule, such as Varicella (chicken pox), hepatitis B and Pneumococcal vaccine (for another type of bacterial brain, blood and ear infection). The next decade will witness a major reduction of these serious childhood infections.

In the future, we shall see vaccines against respiratory infections and diarrhea, and combination vaccines that will reduce the number of injections needed to protect our children and grandchildren. It is only through the widespread use of these vaccines that we can protect our children. Even as the cases of these diseases decrease, unimmunized children still get seriously ill from these infections. Until the diseases are eliminated, as we did with smallpox, we must all ensure the success of universal vaccination to protect all of our children.

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Autism and Vaccines

by Sharon Humiston, MD

It has been hypothesized that the MMR vaccine causes autism. This hypothesis has received a great deal of media coverage - so much so that a parent of an autistic child remarked to me that it was "common knowledge" that MMR causes autism. Most physicians and scientists would disagree.

The debate limps on. In April, 2000, the Committee on Government Reform began hearing testimony on autism and vaccines from parents, scientists and public health officials. In mid-June, 2000, the American Academy of Pediatrics will review the scientific evidence on the matter. These efforts, however, are just the debate's opening ceremonies. We are a long way from understanding autism or its causes.

The array of terms that people use to refer to autism and autism-like disorders contribute to the bewilderment. Pervasive Developmental Disorder, or PDD, has two main groupings:

· The SPECIFIED pervasive developmental disorders include Asperger's syndrome and autistic disorder, as well as several less closely related neurologic disorders such as Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder. Asperger's syndrome is often thought of as mild autism because, affected children have narrow areas of interest and poor social skills, but no noticeable language delay.

· The terms Pervasive Developmental Disorder - NOT OTHERWISE SPECIFIED (PDD - NOS) and atypical PDD are often used to mean that a patient has some, but not all the criteria for autism. Synonyms include autistic tendencies, autistic-like behavior, or autism spectrum disorder.

What is autism?

Autism is a neurologic disorder. Its components include:

· Marked impairment in social interaction. For example, autistic children in day care may gaze absently out the window instead of participating in games.

· Communication. Some autistics have little or no expressive language and may point to what they want with their whole hand instead of using the developmentally more advanced single finger point. Some autistics articulate well, but they are only echoing what the other speaker said. Similarly, autistics may have poor receptive language skills, not comprehending even simple, life-saving commands like "STOP."

· Restricted, repetitive patterns of behaviors, activities, and interests. For example, an autistic child may flick a pencil in front of a light for hours if left undisturbed, may watch the same 5 minutes of the same video over and over, or may escape the house repeatedly to get back to the swimming pool with which they have become obsessed.

The impairments often extend beyond this list. Many autistic children have problems with sensory processing - a host of common sounds, tastes, and textures are experienced as unbearable. For example, autistic children may walk around with their hands over their ears, eat a diet consisting of nothing but apples and spaghetti, or persistently try to remove their clothes. The cerebellum of the brain may be involved and many autistic children love spinning themselves and objects. Indeed, the "pervasive" in "pervasive developmental disorder" is particularly apt.

What causes autism?

A nurse at the hospital where I work speculated, "I think all this autism is being caused by the ultrasounds everyone is getting. How do we know that these aren't disrupting the fetus?" I don't have an answer. The list of chemicals that have been shown to be toxic to the developing brain includes metals (e.g., lead), nicotine, pesticides, solvents, dioxin and PCBs. Data is insufficient to pinpoint which - if any - of these is causing the rise in autism. In fact, in the United States, we are not sure if the proportion of children with autism is really on the rise or if numbers seem to be increasing for other reasons - for example, an increase in the population, a change in the criteria for diagnosing autism, or greater diligence in early developmental screening.

Long before people blamed vaccines for autism, they blamed mothers. Fifty years ago, Bruno Bettelheim advanced the theory that autism was caused by emotionally unavailable mothers. Back then, it was considered "common knowledge" that autistic children needed psychological therapy. Fortunately, almost no one believes the "refrigerator mother" theory anymore - we now know more about the neurologic basis of autism because of pioneering scientists.

Autism may be caused by disordered brain structure. The brains of autistic people, when examined in autopsy or using Magnetic Resonance Imaging, are different from normal brains in important ways. For example, parts of the brain that develop during gestation - possibly as early as the 20th to 24th DAYS of gestation - were found to be damaged.

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This explains why one-third of fetuses exposed to Thalidomide (a medication that is no longer on the market) during this crucial phase of pregnancy grew into autistic children. Similarly, a fetus that survives a German measles infection, a vaccine-preventable condition, is at increased risk for autism.

Autism may be caused by disordered brain chemistry. Neurotransmitters are the chemicals produced by nerve cells to pass messages from one nerve cell to the next. One such neurotransmitter is serotonin, which controls, for example, sleep, moods, and some types of sensory perceptions. Autistics tend to have elevated serotonin levels and corresponding disturbances.

What could cause disordered brain structure and/or brain chemistry? Genes. The genetics of autism are not fully understood, but there is strong evidence of a genetic component. A family with one autistic child has a 3 to 4.5 percent chance of having a second child with autism. This is 50 times the normal risk. In 1997 a group of genetic researchers announced they had located 3 to 5 genes on chromosomes 7 and 16 that they believe cause most autism spectrum disorders. It is important to realize that if one (genetically) identical twin is autistic, the other has a 75 percent chance of being affected, whereas only three percent of non-identical twins are both affected. While genetics must play an important role, the presence of identical twins who are not both affected points to a co-contributor. It is not known if this other factor is, for example, an infection or an environmental toxin. Some people believe that the other factor is vaccination.

Some day, if we fund the studies necessary to really understand autism, we may be capable of differentiating autism and the autism spectrum disorders more finely into sub-categories and of understanding the causative factors within each subset. This detailed understanding is crucial to the design and evaluation of therapy and to the development of primary and secondary prevention.

Why blame vaccines?

In a world full of developmental neurotoxicants, why blame vaccines? The main reason is some parents report that "shortly" (which can range from days to months) after the MMR vaccination they saw the first signs of autism. In general, parents' observations are worth taking seriously. On the other hand, there are some features of vaccines that make them stand out in parents' minds as "usual suspects" when a health problem arises. Primarily, vaccines just seem unnecessary because they have been so successful at decreasing disease rates.

Additionally, vaccines are:

· man-made, which makes them scarier than something "natural" like the viruses that circulate throughout the world

· episodic, which makes them scarier than something we live with all the time like pollution

· mandatory, which makes them scarier than something we choose to use like glues and cleaning solutions

· memorable, which makes them scarier than something we don't notice like dioxins and PCBs.

Because babies cry before, during, and after vaccination, the process is a much more unpleasant memory than prenatal ultrasound.

These are not new features of vaccination and they have not made the news. What did make the news (and the speakers' circuit) was a 1998 "Early Report" in the Lancet (Volume 351, February 28) in which a team from the Royal Free Hospital and School of Medicine in London found 12 patients who had both intestinal abnormalities and neuropsychiatric dysfunction. Nine of the 12 had autism. For eight of the 12 patients the neuropsychiatric symptoms were preceded by MMR vaccination. The researchers speculated that:

· the MMR vaccine caused changes in the bowel wall, which in turn led to

· functional vitamin B12 deficiency (actual vitamin B12 levels were normal) OR excessive absorption of neurologically active peptides (in this case breakdown products of barley, rye, oats, and casein from milk and dairy products) OR both, and this led to

· developmental regression in several forms, including autism.

The news, however, did not pick up the part in the article where the researchers stated, "We did not prove an association between measles, mumps and rubella vaccine and the syndrome described." It was only an early report - not a large, controlled, blinded study. It was published to stimulate thought and further research. Dr. Wakefield, the lead researcher on the 1998 article, now speculates that the mercury-based preservative in first year vaccines damages the immune system - although the child does not appear ill or prone to infection. The damaged immune system does not kill off the live weakened measles virus in MMR - yet it keeps it under check enough that full-fledged, overwhelming infection is not noted. Dr. Wakefield also still believes the measles vaccine virus attacks the intestinal walls causing a "leaky gut" and consequent developmental regression.

Some researchers have found evidence that this elaborate chain is unlikely.

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"It is a riddle wrapped in a mystery inside an enigma."

Winston Churchill

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Evidence for the defense:

The study reported in the 1999 Lancet article by Brent Taylor, et al (Volume 353, June 12) utilized the U.K.'s special needs/disability registers and special schools in eight health districts. Clinical records were linked to immunization registry records. While a steady increase in autism was noted in the U.K., no "step-up" in the increase was noted when MMR was introduced. The mean age at the autism diagnosis was the same whether children received MMR before 18 months of age, after 18 months of age, or not at all; we'd expect that if MMR were causing autism the developmental delay would be diagnosed earlier in children who received the vaccine earlier. They also showed that even when vaccination rates had leveled off the apparent increase in autism persisted. This is not particularly good news, but it contributes to the exoneration of the vaccine.

The alternative to vaccination

Until we eradicate measles, the alternative to vaccination is disease. This is not theoretical. Only a decade ago in the United States 123 people died of measles over a three year period. That's not speculation; you can count the death certificates.

I read an account written by a nurse explaining how the idea that post-vaccinal autism was completely feasible. She hypothesized a vaccine-induced occult encephalitis that left the child with developmental delays. Encephalitis is indeed a recognized rare side effect of measles vaccine, but it is noticeable, not something you'd be too busy to bring to medical attention. If we are worried about encephalitis we will keep using the vaccine; 2-out-of-1000 children with natural measles develop encephalitis, an incidence many fold higher than after the vaccine.

Summary

To review, autism is a pervasive development disorder with marked impairment in social interaction and communication as well as restricted, repetitive patterns of behaviors, activities, and interests. The basis of autism is differences in the brains of autistic people - both structural and neurotransmitter differences. Both of these probably reflect genetic disorders.

Toxic insults - such as a rubella infection or Thalidomide early in pregnancy can also cause autism. Theories about the interaction of genetics and environmental factors are being explored.

Could MMR or measles vaccine contribute in some way? So far, the epidemiologic evidence is against this theory. In fact, at this time, there is no good scientific evidence that implicates MMR or measles vaccine. Further studies are underway.

Autism is a tragedy for everyone involved. There are few reliable roads to true understanding that will, in turn, lead to prevention. Good science is the most reliable road to this understanding.

As a parent of an autistic son I am disturbed at the way the debate is being framed - as valiant, insightful parents vs. the bombastic, uncaring scientific establishment, as the daring people with The Answer ("MMR causes autism and should be abandoned") vs. the blind fools who are unwilling to accept this truth. Let me say this clearly:

1. We DO NOT have the answer. More study is needed. We must not accept this early report as being the complete story.

2. The greatest hope for my son and my daughter's unborn children lies in the hands of scientists. Let them turn their microscopes on me and my genes and everything I breathed, drank, and ate during pregnancy and everything to which my brown-eyed baby was exposed.

3. Autism is a messy, inconvenient disorder for research. It's ill-defined and multi-faceted. It is essential that parents keep voicing the need for further research and monitoring to be sure money earmarked for autism research is used to maximal effect.

Unfortunately, science is not cheap, easy, or quick. If we are serious about uncovering the causes of autism, we must not grasp at the first or most convenient theory. We cannot stop with intuition or temporal association. We must make a commitment to the scientific process - and the associated expenditures - that have led to other triumphs of prevention we enjoy in this age.

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Recommended Childhood Immunization Schedule: 1985

Age / Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	24 mos	4-6 yrs	11-12 yrs	14-16 yrs
Diphtheria, Tetanus, Pertussis			DTP	DTP	DTP			DTP	DTP			Td
Polio			OPV	OPV				OPV		OPV		
Measles, Mumps, Rubella							MMR					

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