not uncommonly reactions to pertussis vaccine such as a swollen injection area and some fever. Occasionally, there was severe plain from the site of the injection, and on rare occasions convulsions, high fever and the neurological sequelae of brain hemorrhage, hemiplegia and mental retardation, just as with the disease itself. The cause of these neurological manifestations following the use of pertussis vaccine is not definitely known either on a pathological, histological or clinical basis. These manifestations, however, were first brought to the attention of the medical profession in April of 1948. Thereafter there were developed additional controls over the production of pertussis vaccine. Under the new regulations the encephalopathic type of reaction was minimized. The use of phosphate adjuvants [7] made possible a decrease in the amount of pertussis in the formula; new maximum as well as minimum potency standards were set; and the toxicity of the pertussis component was reduced by extra heating and by the toxicity test. The potency test is performed by injecting groups of mice with varying dilutions of vaccine, and, then, after a period of time, challenging the mice with virulent organisms. The toxicity test was performed by injecting a group of ten mice of specified weight with a specified dose of vaccine and weighing the group at specified intervals. I will have further occasion herein to discuss in greater detail the matter of tests as to their adequacy in the present case. Mention has been made above of the use of phosphate adjuvants which permitted a reduction of the amount of pertussis in the formula. Today, at least in American vaccines, an aluminum salt is used as an adjuvant. An adjuvant serves as a depot or button which will slow the release of the antigen rather than having it released all at once when the vaccine is merely suspended in a liquid. When aluminum phosphate was first used, there was some apparent increase in toxicity and the amount of the aluminum phosphate was reduced approximately one-half with a resultant substantial reduction in toxicity. Thereafter vaccines with the aluminum phosphate were no more toxic than other adsorbed vaccines.

One other aspect of the manufacture of pertussis vaccine should be mentioned at this time. All vaccines packed in multi-dose vials require a preservative to keep them sterile (not to preserve their potency). In the development of pertussis vaccines until the development of polio vaccine the universal preservative used was Merthiolate. At the time there was no information that the Merthiolate affected the vaccine for better or for worse, but it has recently been discovered that Merthiolate acts as a stabilizer of the vaccine, that in its presence the vaccine tends to decrease in toxicity in storage at the same time that its potency is stabilized at a level at least for the first six months.

In the early 1940's, there was developed the method of combining pertussis vaccine with diphtheria and tetanus toxoid into a combined antigen product colloquially known as "DDT". No apparent decrease in toxicity or reactivity was noted as a result of such combination. Defendant marketed such a product under the trade name "Triogen".

After the Salk poliomyelitis vaccine had been developed, it was decided by defendant to attempt to mix the polio vaccine with the "Triogen" in order to develop commercially a quadruple antigen product. In connection with the development of polio vaccine it had been learned that Merthiolate had a deleterious effect upon the polio virus, caused by the action of released mercury ions. Eli Lilly & Company incorporated Versene within its vaccine, which prevented the release of the mercury ions. However, Versene was incompatible with the aluminum phosphate used as an adjuvant by defendant in Triogen, and since defendant anticipated that it would want to develop a vaccine combining the polio vaccine with Triogen, it decided to use benzethonium chloride, or Phemerol which was defendant's trade name for this product.

Unknown to defendant the benzethonium chloride had an unusual effect on the pertussis vaccine contained therein. It appears that there was a loss of potency, a reduction in the protective activity of the pertussis vaccine when benzethonium chloride rather than Merthiolate was used as the preservative. This loss occurred only when the vaccine was exposed to variations in temperature. While there is no knowledge as to the manner in which benzethonium chloride affects the unidentified protective antigen of the pertussis vaccine, considerable knowledge has been accumulated as to the physical effects of benzethonium chloride on pertussis bacteria placed in a solution including benzethonium

[7] An adjuvant in immunology is any substance that, when mixed with an antigen, enhances the antigenicity and gives a superior response.