March 20, 1957.

SPECIFICATION

The invention herein described relates to a composite vaccine which comprises a killed virus and an antibody which is specific for the killed virus. The antibody can be obtained from animals by injecting them with the killed virus; it can also be obtained from humans who have recovered from the virus disease and who have been injected with the killed virus for the purpose of raising the antibody titer in the serum.

Composite vaccines of this type, when injected intradermally (or in conjunction with an adjuvant subcutaneously) can confer lasting disease resistance (approximating the disease resistance which is conferred by the disease itself).

The class of virus diseases in which vaccination by such a composite vaccine is indicated, consists of those virus diseases where -

a) the disease itself causes lasting immunity;

b) the intestinal mucosa or the mucosa of the respiratory tract (including the nasal mucosa) are invaded by the virus in the initial phase of the disease.

An example of a disease which falls into this class, is polio myelitis. In the case of poliomyelitis vaccination by the currently used killed vaccine (Salk vaccine) does not confer on the patient the disease resistance which is conferred on patients by the disease itself. This type of vaccination may greatly raise in the vaccinated individual the titer of the circulating antibody ~~also~~ against the polio virus. But if such an individual, who had no previous contact with live polio virus, is infected through the oral route by live polio virus so that the intestinal mucosa are

invaded by the virus and the intestinal phase of the disease is initiated, this phase of the disease has about the same intensity and duration as in an invaccinated individual. Therefore, a population which has been immunized through Salk vaccination continues to be subject to the intestinal polio epidemics. Those individuals in the population who have been Salk vaccinated and have a high titer of circulating antibody will be protected by this antibody against the spreading of the disease from the intestinal tract to the nervous system. - Individuals, however, who are not Salk vaccinated - even though they live within a population where most of their fellow citizens have been vaccinated - have about the same chance of paralytic polio as individuals who live within a comparable unvaccinated population.

In contrast to a person who had never had contact with live polio virus but has been Salk vaccinated, a person who has been infected through the oral route with live polio and who has gone through the intestinal phase of this disease, has thereby acquired disease resistance not possessed by the former. If the latter is infected with polio through the oral route, the intestinal phase of the disease will be very much shorter than in the former one, who, if infected with polio through the oral route, will go through the intestinal phase of the disease with approximately the same intensity and duration as an unvaccinated person who had not been previously exposed to polio.

— Insert I

According to this invention, intracutaneous injections of the composite vaccine which comprises killed polio virus and antibody against polio virus, can confer approximately the

same disease resistance on an individual as does the disease itself. Injecting such a composite vaccine - together with an adjuvant - subcutaneously, can also confer such disease resistance. If an individual who has been Salk vaccinated and as a result of this vaccination has high titer of circulating antibodies against the polio virus, is also made disease resistant by being inoculated with the composite vaccine, then he is - in case of an oral infection with live polio virus

a) protected against the spread of the virus from the point of entry to the nervous system, and

b) the intestinal phase of the disease will be about as weak and as short as if he had had a previous intestinal infection.

Uhr, J.W., Salvin, S.B. and Pappenheimer,A.M.,Jr., Journal of Experimental Medicine, Vol. 105 (1957) have described how by injecting intracutaneously a mixture of diphteria toxoid and a four-fold excess of antibody will produce, in unsensitized individuals, strong delayed hyper sensitivity without evoking an early rise in the titer of circulating antibodies against diphteria toxoid. In the case of diphteria toxoid, the delayed type hyper-sensitivity can be also evoked by injecting the mixture of toxoid and antibody -- together with an adjuvant -- sub-cutaneously.

According to this invention an adequate level of disease resistance against polio is produced through the injection intracutaneously (or - with an adjuvant - subcutaneously) if the same amount of killed polio virus and the same manner of injection is used, that would lead -- using diphteria toxoid

in lieu of killed polio virus -- to a maximal degree of delayed type hyper-sensitivity against diphteria toxoid.

Insert on Page 3 -

In order to perform the test ovalbumine (or diphteria toxoid) is substituted for the killed virus in the composite vaccine, and antiserum against ovalbumine (or diphteria toxoid) is substituted for antibody against the killed virus in the composite vaccine. The test consists in determining whether this substituted composite vaccine, if injected in a given manner, evokes hyper-sensitivity of the delayed type.

Whether this substitute composite vaccine evokes hyper-sensitivity of the delayed type can be tested in either of two ways:

Witnessed - March 23, 1957.

Carol Andrén

March 22, 1957.

SPECIFICATION

The currently used poliomyelitis vaccinations by killed virus (Salk vaccine) do not confer on the patient the disease resistance which is conferred by the disease itself. This type of vaccination may greatly raise in the vaccinated individual the titer of the circulating antibody against the polio virus. But if such an individual, who had no previous contact with live polio virus, is infected through the oral route by live polio virus so that the intestinal mucosae are invaded by the virus and the intestinal phase of the disease is initiated, this phase of the disease has about the same intensity and duration as in an unvaccinated individual. Therefore, a population which has been immunized through Salk vaccination continues to be subject to the intestinal polio epidemics. Those individuals in the population who have been Salk vaccinated and have a high titer of circulating antibody will be protected by this antibody against the spreading of the disease from the intestinal tract to the nervous system. Individuals, however, who are not Salk vaccinated - even though they live within a population where most of their fellow citizens have been vaccinated - have about the same chance of paralytic polio as individuals who live within a comparable unvaccinated population.

In contrast to a person who had never had contact with live polio virus but has been Salk vaccinated, a person who has been infected through the oral route with live polio and who has gone through the intestinal phase of this disease, has thereby acquired disease resistance not possessed by the former. If the latter is infected with polio through the oral route, the intestinal phase

of the disease will be very much shorter than in the former one who, if infected with polio through the oral route, will go through the intestinal phase of the disease with approximately the same intensity and duration as an unvaccinated person who had not been previously exposed to polio).

The polio virus is one of the viruses of a group called D.R. viruses, the members of which have the following characteristics in common:

a) there is an initial phase of the disease in which the intestinal mucosa or the mucosa of the respiratory tract (including the nasal passages) are affected;

b) the disease causes lasting disease resistance in the sense that on a subsequent infection the initial phase is either completely suppressed or weakened and shortened in its duration.

Vaccination with the killed virus in the manner which is currently practised in the case of poliomyelitis (Salk vaccine) - even though it may lead to a high titer of circulating antibodies - does not cause lasting disease resistance with respect to shortening the initial phase of the disease in which the intestinal mucosa or the mucosa of the respiratory tract are affected.

According to this invention it is possible to produce such disease resistance in the above defined group of viruses (over and above the kind of immunity conferred on the patient by the circulating antibodies) by vaccinating the patient with a composite vaccine. This composite vaccine contains killed virus and either an antibody which is specific for the killed virus, or an adjuvant, or both, and it produces disease resistance which is specific to the killed virus used if injected in the manner described below.

The composition of the vaccine and the manner in which it is injected will produce disease resistance in every case when the following conditions are satisfied: if the killed virus is replaced by about the same quantity of either ovalbumine or diphteria toxoid, and if the antibody against the virus is replaced by an antibody against ovalbumine or diphteria toxoid, and if the composite vaccine which is thus substituted is injected in a manner in which a high degree of hyper-sensitivity of delayed type is evoked against ovalbumine or against diphteria toxoid, respectively, then according to this invention the composite vaccine injected in the same manner, will produce disease resistance.

This provides a comparatively simple test that permits us to determine in advance whether the given composite vaccine containing killed virus, if injected in a given manner, may or may not be expected to produce disease resistance. ~~Whether either test which is carried out by substituting either albumine or diphteria toxoid in the above stated manner for the killed virus produces hyper-sensitivity of the delayed type can be tested in either of two ways:~~

a) if the composite vaccine containing ovalbumine or diphteria toxoid does not evoke circulating antibodies, then the presence of delayed hyper-sensitivity can be determined by injecting ovalbumine (or diphteria toxoid) into the skin of the test subject;

b) if the composite vaccine containing ovalbumine (or diphteria toxoid) evokes an early appearance of circulating antibodies in the test individual, then the absence of hyper-sensitivity may be determined by transferring lymphocytes to the second test individual and then skin test the second test individual with ovalbumine (or diphteria toxoid).

It is established that delayed type of hyper-sensitivity can be evoked by injecting ovalbumine (or diphteria toxoid) mixed with antibody (about a four-fold excess of antibody may be used) and evoke delayed type hyper-sensitivity against ovalbumine (or diphteria toxoid) without giving rise to an early appearance of circulating antibodies. In these cases the appearance of delayed type hyper-sensitivity subsequent to the injection, can be ascertained by skin testing the injected test subject. Experiments of this type have established that intracutaneous injection of 30 microgram of diphteria toxoid or ovalbumine in the form of an antigene-antibody precipitate containing a four-fold excess of antibody, will produce delayed type hyper-sensitivity when injected intracutaneously (in 10 portions of .1 cc each).

Such antibody precipitates mixed with complete Freund adjuvant injected in adequate quantity subcutaneously, will also evoke delayed type hyper-sensitivity. In neither of these two cases is there an early appearance of circulating antibody against ovalbumine (or diphteria toxoid).

If an excess of antigene over an antibody is used and if an adequate amount is injected subcutaneously mixed with complete Freund adjuvant, circulating antibodies against ovalbumine (or diphteria toxoid) will be produced. This makes it difficult to determine by direct skin test on the injected individual that hypersensitivity of the delayed type against ovalbumine (or diphteria toxoid) is produced. This, however, can be shown to be the case by transferring lymphocytes to a second test subject and by skin testing the second test subject.

According to this invention, in the case of the ~~injecting a composite vaccine containing a killed virus of the D.R. group and in~~ viruses of the D.R. group and in particular the polio virus

particularly injecting a composite vaccine constituted as described above and injected in the manner described above but substituting the killed virus for ovalbumine and substituting antibody against the killed virus for antibody against ovalbumine and using the above mentioned proper route of injection in each given case, will lead to disease resistance that will approximate the disease resistance that ensues following an intestinal infection by the live virus.

Thus injecting intracutaneously 30 microgram of killed polio virus (Salk vaccine) mixed with antibody against the killed polio virus (four-fold excess), will lead to a high level of disease resistance against polio approximating the disease resistance conferred by an intestinal infection with live virus.

If an individual who has been Salk vaccinated and as a result of this vaccination has high titer of circulating antibodies against the polio virus, is also made disease resistant by being inoculated with this composite vaccine, then he is - in case of an oral infection with live polio virus -

a) protected against the spread of the virus from the point of entry to the nervous system; and
b) the intestinal phase of the disease will be about as weak and as short as if he had had a previous intestinal infection with live virus.

In preparing the composite vaccine which contains antibody but does not necessarily contain adjuvant ~~and which must be injected intracutaneously~~ it is desireable to use antibodies contained in human sera rather than antibodies obtained from animal sera.

Witnessed -March 22,1957:

Carol Andrén

The amount of antibody against the virus present in the human serum can be essayed as follows: One prepares a series of samples using the same quantity of virus in each sample with increased amounts of ~~serum~~ antiserum in subsequent samples. Each subsequent sample which is injected, may contain twice as much antiserum as the preceding sample. Each of these samples is injected ~~intradermally~~ into a monkey that has not been previously exposed to polio. The monkeys which have been injected with a sample that contained low amounts of serum will respond with early production of circulating antibody. The sample injected in the first of the monkeys of the series which does not respond with early production of circulating antibody, contains a slight excess of antibody over the killed virus and thus determines the antibody titer of the serum ~~used~~ for the purposes of preparing the composite vaccine. The remaining monkeys in the series that have been injected with samples containing higher amounts of antibody serve as controls. They must show no early formation production of circulating antibody if the essay is to be valid.

Such an essay permits us to prepare a composite vaccine composed of killed polio virus and a slight excess of antibody against the polio virus. Such a composite vaccine if injected in adequate amounts intracutaneously will confer disease resistance on the patient.

By injecting subcutaneously an adequate amount of killed polio virus (Salk vaccine) mixed with complete Freund adjuvant, both circulating antibody and disease resistance can be induced at the same time. The same holds if antibody is present in this composite vaccine containing complete Freund adjuvant, ~~it is preferable to have an~~

Insert

Such a composite vaccine may contain, in addition to the killed polio virus and antibody to the killed polio virus, an adjuvant such as an oil water emulsion. High level of disease resistance is obtained if 30 microgram of killed polio virus and an excess of antibody against the polio virus are injected intracutaneously in an oil water emulsion.

If it is desired to evoke also circulating antibodies of sufficient ~~xisx~~ titer as well as disease resistance with the same injection, a two-fold excess of killed polio virus over the antibody may be injected intracutaneously. A certain level of disease resistance is obtained through intracutaneous injections of such a composite vaccine (containing both killed polio virus and adjuvant) even if no antibody is present in the composite vaccine.

provided there is an
excess of Salk vaccine over the antibody against killed polio virus. A five-fold excess of killed polio virus over the antibody is adequate to produce high titer of circulating antibodies, if the amount injected is sufficient to produce a high level of disease resistance.

Concerning the state of the art in respect to evoking hyper-sensitivity of the delayed type I refer to Uhr, J.W., Salvin, S.B. and Pappenheimer,A.M.Jr., Journal of Experimental Medicine, Vol. 105 (1957), and to Lawrence, H.S., and Pappenheimer, A.M.Jr., Journal of Experimental Medicine, Vol. 104, (1956).

Witnessed - March 22,1957:

Carol Andrén

3) A therapeutic preparation for intracutaneous injection comprising a killed virus of the D.R. group of viruses and an adjuvant such as an oil water emulsion;

4) A therapeutic preparation for intracutaneous injection comprising killed polio virus and an adjuvant such as an oil water emulsion;

5) A therapeutic preparation for intracutaneous injection comprising a killed virus of the D.R. group of viruses; antibody against the killed virus and an adjuvant such as an oil water emulsion;

6) A therapeutic preparation for intracutaneous injection comprising killed polio virus, antibody against polio virus and an adjuvant such as an oil water emulsion.

C L A I M S:

I claim -

1) A therapeutic preparation comprising a killed virus of the D.R. group of viruses and antibody against the said virus - the said therapeutic preparation representing a composite vaccine suitable for intracutaneous injection;

2) A therapeutic preparation comprising a killed polio virus and antibody against the said polio virus - the said therapeutic preparation representing a composite vaccine suitable for intracutaneous injection;

3) A therapeutic preparation comprising a killed virus of the D.R. group of viruses and complete Freund adjuvant (comprising an oil-water suspension and mycobacteria) - the said therapeutic preparation representing a composite vaccine suitable for injection;

4) A therapeutic preparation comprising a killed polio virus and complete Freund adjuvant (comprising an oil-water suspension and mycobacteria) - the said therapeutic preparation representing a composite vaccine suitable for injection;

5) A therapeutic preparation comprising a killed virus of the D.R. group of viruses, antibody to the said virus and complete Freund adjuvant (comprising an oil-water suspension and mycobacteria) - the said therapeutic preparation representing a composite vaccine suitable for injection;

6) A therapeutic preparation comprising a killed polio virus, antibody to the polio virus and complete Freund adjuvant (comprising an oil-water suspension and mycobacteria) - the said therapeutic preparation representing a composite vaccine suitable for injection.

Witnessed - March 22, 1957.

Carol Andrén

H-20

New York, January 10, 1957.

Agents for Producing Disease Resistance

by Leo Szilard.

This invention relates to agents which if injected are capable of producing increased resistance to the disease for which the agent is specific.

In order to illustrate the principle which is involved I cite the following example:

In the case of infantile paralysis we can distinguish between immunity to the disease and resistance to the disease. By immunity we mean the following: If an individual who has never been infected with live virus, is injected with the killed virus (Salk vaccine) he will produce circulating antibodies. He may then be regarded as immune. On a subsequent infection by live polio virus through the intestinal tract hee will show no resistance to the disease in the sense that virus will be able to grow in the intestinal mucosa, and this phase of the disease will not be affected by the circulating antibodies. As a result of the infection the titer of the circulating antibodies may be further increased (booster effect) and the circulating antibodies may prevent the spread of the disease through the blood circulation from the intestinal mucosa to the brain.

In contrast to the individual who had never been infected with live polio virus but who has been made immune through vaccination with the killed virus and who, therefore, is immune but does not possess resistance to the disease as explained above, an individual who has been infected with the live virus has thereby acquired both immunity and resistance to the disease. Upon a subsequent infection with the live virus the intestinal disease is

Witnessed - January 10,1957

Carol Andrén

Leo Szilard

resisted in the sense that the virus survives in the intestinal mucosa for a period of time which is much shorter than the survival time of the virus in an individual who is immune but not resistant.

It has been proposed to make individuals resistant to polio virus by first making them immune through the injection of Salk vaccine and subsequently infecting them with the live (attenuated) polio virus. According to this invention the same result can be accomplished by injecting into an individual (who has been previously immunized by means of using the Salk vaccine) a mixture of the killed virus (for instance Salk vaccine) and an excess of antiserum or antibody to the killed virus. The antibody to the killed virus can be obtained by immunizing horses or humans, preferably through repeated injections, with the killed polio virus. From the serum thus obtained from humans or horses the antibody can be concentrated in the customary manner, and the agent for producing resistance to polio myolitis is obtained by mixing the killed polio virus with an excess of the specific antibody. Persons who are made disease resistant by ~~repeated~~ injections / of a sufficient dose (or repeated doses) of this agent (to which we shall refer below as DR agent to indicate that it confers disease resistance) will show resistance to polio myolitis in the following sense: if they are infected with live polio virus (of the strain for which the DR agent is specific) they show a much shorter course of the intestinal phase of the disease, i.e. the virus disappears from the intestine much faster than would be the case for persons who have never been infected with the live virus, and may or may not have been immunized by the injection of the killed virus (Salk vaccine).

Witnessed - January 10, 1957.

Carol Andrén

Dr Lenhard

The above example is a special case of a more general principle. There are a number of known diseases where the first phase of the disease consists in the invasion of the intestinal nasal or bronchial mucosa by an infectious agent (such as for instance a virus or a microbe) and this first phase of invasion may or may not be followed by a systematic invasion through the route of the blood circulation (viremia or bacteremia). Many of these diseases confer resistance to the individual for a shorter or longer period of time. During this period of resistance renewed exposure to the same infectious agent leads to a disease which is milder and of shorter duration. According to this invention such resistance can be conferred on an individual by injecting a mixture of either the killed infectious agent (or else a suitable antigen extracted from the infectious agent) and an excess of antibody which is specific for this infectious agent.

Prior to injecting the DR agent thus obtained one may, if one wishes, first immunize the individual against the infectious agent by vaccinating him with the killed infectious agent alone, i.e. one may, as mentioned in the above quoted example, inject the DR agent for polio into individuals who have been previously made immune to polio by means of the Salk vaccine.

The importance of conferring disease resistance to the individual by means of a DR agent according to the invention here described, is not as great in the case of polio myolitis as it is in those other diseases where the primary phase of the invasion by the infectious agent causes a serious disturbance such as for instance in typhoid fever or infections by certain other enteric pathogenic organisms.

Witnessed January 10, 1957.

Carol Andrén

I claim a product adapted to be used as a DR agent for a specific disease which consists of a mixture of a quantity of the killed infectious agent of the disease (or an extract thereof which contains the relevant antigens) and a quantity of antiserum specific for this infectious agent (or a fraction of such antiserum which contains the relevant antibodies), the ratio of antibodies to antigens being large enough for the antibodies to saturate the antigens.

New York, January 10, 1956.

Leo Szilard

Witnessed: January 10, 1957.

Carol Andrén

The amount of antibody against the virus present in the human serum can be essayed as follows: One prepares a series of samples usimg the same quantity of virus in each sample with increasing amounts of antiserum in subsequent samples. Each subsequent sample which is injected, may contain twice as much antiserum as the preceding sample. Each of these samples is injected into a monkey that has not been previously exposed to polio. The monkeys which have been injected with a sample that contained low amounts of serum will respond with early production of circulating antibody. The sample injected in the first of the monkeys of the series which does not respond with early production of circulating antibody, contains a slight excess of antibody over the killed virus and thus determines the antibody titer of the serum for the purposes of preparing the composite vaccine. The remaining monkeys in the series that have been injected with samples containing higher amounts of antibody serve as controls. They must show no early formation production of circulating antibody if the essay is to be valid.

Such an essay permits us to prepare a composite vaccine composed of killed polio virus and a slight excess of antibody against the polio virus. Such a composite vaccine if injected in adequate amounts intracutaneously will confer disease resistance on the patient.

Soch a composite vaccine may contain, in addition to the killed polio virus and antibody to the killed polio virus, an adjuvant such as an oil water emulsion. High level of disease resistance is obtained if 30 microgram of killed polio virus and an excess of antibody against the polio virus are injected intra-

Witnessed - March 27, 1957

Carol Andren

cutaneously in an oil water emulsion.

If it is desired to evoke also circulating antibodies of sufficient titer, as well as disease resistance, with the same injection, a two-fold excess of killed polio virus over the antibody (plus adjuvant) may be injected intracutaneously. A certain level of disease resistance is obtained through intracutaneous injections of such a composite vaccine (containing both killed polio virus and adjuvant) even if no antibody is present in the composite vaccine.

By injecting subcutaneously an adequate amount of killed polio virus (Salk vaccine) mixed with complete Freund adjuvant, both circulating antibody and disease resistance can be induced at the same time. The same holds if antibody is present in this composite vaccine containing complete Freund adjuvant, provided there is an excess of Salk vaccine over the antibody against killed polio virus. A two-fold excess of killed polio virus over the antibody is adequate to produce high titer of circulating antibodies, if the amount injected is sufficient to produce a high level of disease resistance.

Concerning the state of the art in respect to evoking hyper-sensitivity of the delayed type I refer to Uhr, J.W., Salvin, S.B. and Pappenheimer, A.M.Jr., Journal of Experimental Medicine, Vol. 105 (1957), and to Lawrence, H.S., and Pappenheimer, A.M.Jr., Journal of Experimental Medicine, Vol. 104, (1956).

Witnessed - March 27, 1957.

Carol Andren

Robert Leonard

C L A I M S:

I claim -

1) A therapeutic preparation for intracutaneous injection comprising a killed virus of the D.R. group of viruses and antibody against the said virus;
2) A therapeutic preparation for intracutaneous injection comprising a killed polio virus and antibody against polio virus;
3) A therapeutic preparation for intracutaneous injection comprising a killed virus of the D.R.group of viruses and an adjuvant such as an oil-water emulsion;
4) A therapeutic preparation for intracutaneous injection comprising killed polio virus and an adjuvant such as an oil water emulsion;
5) A therapeutic preparation for intracutaneous injection comprising a killed virus of the D,R. group of viruses; antibody against the said killed virus and an adjuvant such as an oil water emulsion;
6) A therapeutic preparation for intracutaneous injection comprising killed polio virus, antibody against polio virus and an adjuvant such as an oil water emulsion;
7) A therapeutic preparation for parenteral injection comprising a killed virus of the D.R. group of viruses and complete Freund adjuvant (comprising an oil water suspension and mycobacteria);
8) A therapeutic preparation for parenteral injection comprising a killed polio virus and complete Freund adjuvant (comprising an oil water suspension and mycobacteria);
9) A therapeutic preparation for parenteral injection comprising a killed virus of the D.R. group of viruses, antibody to the said virus and complete Freund adjuvant (comprising an oil-water suspension and mycobacteria);
10) A therapeutic preparation for parenteral injection comprising killed polio virus, antibody to polio virus and complete Freund adjuvant (comprising an oil-water suspension and mycobacteria).

Witnessed - March 27, 1957.

Carol Andrén

New York, January 10, 1957.

Agents for Producing Disease Resistance

by Leo Szilard.

This invention relates to agents which if injected are capable of producing increased resistance to the disease for which the agent is specific.

In order to illustrate the principle which is involved I cite the following example:

In the case of infantile paralysis we can distinguish between immunity to the disease and resistance to the disease. By immunity we mean the following: If an individual who has never been infected with live virus, is injected with the killed virus (Salk vaccine) he will produce circulating antibodies. He may then be regarded as immune. On a subsequent infection by live polio virus through the intestinal tract he will show no resistance to the disease in the sense that virus will be able to grow in the intestinal mucosa, and this phase of the disease will not be affected by the circulating antibodies. As a result of the infection the titer of the circulating antibodies may be further increased (booster effect) and the circulating antibodies may prevent the spread of the disease through the blood circulation from the intestinal mucosa to the brain.

In contrast to the individual who had never been infected with live polio virus but who has been made immune through vaccination with the killed virus and who, therefore, is immune but does not possess resistance to the disease as explained above, an individual who has been infected with the live virus has thereby acquired both immunity and resistance to the disease. Upon a subsequent infection with the live virus the intestinal disease is

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Witnessed - January 10,1957

Carol Andrén

Leo Szilard

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Chicago 37, Ill.

Dr. Leo Szilard
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50 Central Park South
New York 19 NY

409

resisted in the sense that the virus survives in the intestinal mucosa for a period of time which is much shorter than the survival time of the virus in an individual who is immune but not resistant.

It has been proposed to make individuals resistant to polio virus by first making them immune through the injection of Salk vaccine and subsequently infecting them with the live (attenuated) polio virus. According to this invention the same result can be accomplished by injecting into an individual (who has been previously immunized by means of using the Salk vaccine) a mixture of the killed virus (for instance Salk vaccine) and an excess of antiserum or antibody to the killed virus. The antibody to the killed virus can be obtained by immunizing horses or humans, preferably through repeated injections, with the killed polio virus. From the serum thus obtained from humans or horses the antibody can be concentrated in the customary manner, and the agent for producing resistance to polio myolitis is obtained by mixing the killed polio virus with an excess of the specific antibody. Persons who are made disease resistant by ~~repeated~~ injections of a sufficient dose (or repeated doses) of this agent (to which we shall refer below as DR agent to indicate that it confers disease resistance) will show resistance to polio myolitis in the following sense: if they are infected with live polio virus (of the strain for which the DR agent is specific) they show a much shorter course of the intestinal phase of the disease, i.e. the virus disappears from the intestine much faster than would be the case for persons who have never been infected with the live virus, and may or may not have been immunized by the injection of the killed virus (Salk vaccine).

Witnessed - January 10, 1957.

Carol Andrén

W. Lenhard

The above example is a special case of a more general principle. There are a number of known diseases where the first phase of the disease consists in the invasion of the intestinal nasal or bronchial mucosa by an infectious agent (such as for instance a virus or a microbe) and this first phase of invasion may or may not be followed by a systematic invasion through the route of the blood circulation (viremia or bacteremia). Many of these diseases confer resistance to the individual for a shorter or longer period of time. During this period of resistance renewed exposure to the same infectious agent leads to a disease which is milder and of shorter duration. According to this invention such resistance can be conferred on an individual by injecting a mixture of either the killed infectious agent (or else a suitable antigen extracted from the infectious agent) and an excess of antibody which is specific for this infectious agent.

Prior to injecting the DR agent thus obtained one may, if one wishes, first immunize the individual against the infectious agent by vaccinating him with the killed infectious agent alone, i.e. one may, as mentioned in the above quoted example, inject the DR agent for polio into individuals who have been previously made immune to polio by means of the Salk vaccine.

The importance of conferring disease resistance to the individual by means of a DR agent according to the invention here described, is not as great in the case of polio myolitis as it is in those other diseases where the primary phase of the invasion by the infectious agent causes a serious disturbance such as for instance in typhoid fever or infections by certain other enteric pathogenic organisms.

Witnessed January 10, 1957.
Carol Andrén

I claim a product adapted to be used as a DR agent for a specific disease which consists of a mixture of a quantity of the killed infectious agent of the disease (or an extract thereof which contains the relevant antigens) and a quantity of anti-serum specific for this infectious agent (or a fraction of such antiserum which contains the relevant antibodies), the ratio of antibodies to antigens being large enough for the antibodies to saturate the antigens.

New York, January 10, 1956.

Leo Szilard

Witnessed: January 10, 1957.

Carol Andrén

As a clarification of the foregoing text relating to Agents for Producing Disease Resistance, I may add the following: The DR agent described will produce the desired effect best if it is injected intradermally, or, if injected subcutaneously it should be injected together with an adjuvant such as for instance Arlacel plus Bayol F. The expression "relevant antigen" on page 4 must be taken to mean surface antigens of the infectious agent, and the expression "relevant antibodies" must be taken to mean antibodies against the surface antigens of the infectious agent.

Witnessed - January 18, 1957.

Carol Andrén

Carol Andrén

New York, January 10, 1957.

Agents for Producing Disease Resistance

by Leo Szilard.

This invention relates to agents which if injected are capable of producing increased resistance to the disease for which the agent is specific.

In order to illustrate the principle which is involved I cite the following example:

In the case of infantile paralysis we can distinguish between immunity to the disease and resistance to the disease. By immunity we mean the following: If an individual who has never been infected with live virus, is injected with the killed virus (Salk vaccine) he will produce circulating antibodies. He may then be regarded as immune. On a subsequent infection by live polio virus through the intestinal tract he will show no resistance to the disease in the sense that virus will be able to grow in the intestinal mucosa, and this phase of the disease will not be affected by the circulating antibodies. As a result of the infection the titer of the circulating antibodies may be further increased (booster effect) and the circulating antibodies may prevent the spread of the disease through the blood circulation from the intestinal mucosa to the brain.

In contrast to the individual who had never been infected with live polio virus but who has been made immune through vaccination with the killed virus and who, therefore, is immune but does not possess resistance to the disease as explained above, an individual who has been infected with the live virus has thereby acquired both immunity and resistance to the disease. Upon a subsequent infection with the live virus the intestinal disease is

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Witnessed - January 10, 1957

Carol Andrén

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1155 East 57th
Chicago 37, Ill

NEW YORK 1, N.Y.
JAN 14
12-PM
1957

FIGHT
INFANTILE PARALYSIS
JC ARCH OF DIMES

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New York 19 N Y

resisted in the sense that the virus survives in the intestinal mucosa for a period of time which is much shorter than the survival time of the virus in an individual who is immune but not resistant.

It has been proposed to make individuals resistant to polio virus by first making them immune through the injection of Salk vaccine and subsequently infecting them with the live (attenuated) polio virus. According to this invention the same result can be accomplished by injecting into an individual (who has been previously immunized by means of using the Salk vaccine) a mixture of the killed virus (for instance Salk vaccine) and an excess of antiserum or antibody to the killed virus. The antibody to the killed virus can be obtained by immunizing horses or humans, preferably through repeated injections, with the killed polio virus. From the serum thus obtained from humans or horses the antibody can be concentrated in the customary manner, and the agent for producing resistance to polio myolitis is obtained by mixing the killed polio virus with an excess of the specific antibody. Persons who are made disease resistant by ~~repeated~~ injection(s) of a sufficient dose (or repeated doses) of this agent (to which we shall refer below as DR agent to indicate that it confers disease resistance) will show resistance to polio myolitis in the following sense: if they are infected with live polio virus (of the strain for which the DR agent is specific) they show a much shorter course of the intestinal phase of the disease, i.e. the virus disappears from the intestine much faster than would be the case for persons who have never been infected with the live virus, and may or may not have been immunized by the injection of the killed virus (Salk vaccine).

Witnessed - January 10, 1957.

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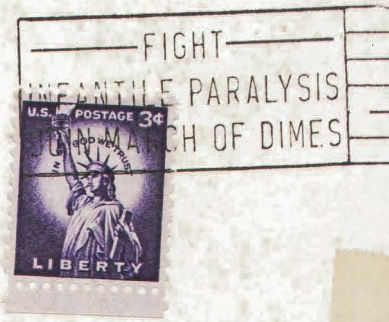

Dr. Leo Szilard
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The above example is a special case of a more general principle. There are a number of known diseases where the first phase of the disease consists in the invasion of the intestinal nasal or bronchial mucosa by an infectious agent (such as for instance a virus or a microbe) and this first phase of invasion may or may not be followed by a systematic invasion through the route of the blood circulation (viremia or bacteremia). Many of these diseases confer resistance to the individual for a shorter or longer period of time. During this period of resistance renewed exposure to the same infectious agent leads to a disease which is milder and of shorter duration. According to this invention such resistance can be conferred on an individual by injecting a mixture of either the killed infectious agent (or else a suitable antigen extracted from the infectious agent) and an excess of antibody which is specific for this infectious agent.

Prior to injecting the DR agent thus obtained one may, if one wishes, first immunize the individual against the infectious agent by vaccinating him with the killed infectious agent alone, i.e. one may, as mentioned in the above quoted example, inject the DR agent for polio into individuals who have been previously made immune to polio by means of the Salk vaccine.

The importance of conferring disease resistance to the individual by means of a DR agent according to the invention here described, is not as great in the case of polio myolitis as it is in those other diseases where the primary phase of the invasion by the infectious agent causes a serious disturbance such as for instance in typhoid fever or infections by certain other enteric pathogenic organisms.

Witnessed January 10, 1957.
Carol Andrén

I claim a product adapted to be used as a DR agent for a specific disease which consists of a mixture of a quantity of the killed infectious agent of the disease (or an extract thereof which contains the relevant antigens) and a quantity of antiserum specific for this infectious agent (or a fraction of such antiserum which contains the relevant antibodies), the ratio of antibodies to antigens being large enough for the antibodies to saturate the antigens.

New York, January 10, 1956.

Leo Szilard

Witnessed: January 10, 1957.

Carol Andrén

As a clarification of the foregoing text relating to Agents for Producing Disease Resistance, I may add the following: The DR agent described will produce the desired effect best if it is injected intradermally, or, if injected subcutaneously it should be injected together with an adjuvant such as for instance Arlacel plus Bayol F. The expression "relevant antigen" on page 4 must be taken to mean surface antigens of the infectious agent, and the expression "relevant antibodies" must be taken to mean antibodies against the surface antigens of the infectious agent.

Witnessed - January 18, 1957.

Carol Andrén

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Leo Szilard

Hotel St. Moritz ; Room 2134
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New York City

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INFORMATION DESK

New York, January 10, 1957.

Agents for Producing Disease Resistance

by Leo Szilard.

This invention relates to agents which if injected are capable of producing increased resistance to the disease for which the agent is specific.

In order to illustrate the principle which is involved I cite the following example:

In the case of infantile paralysis we can distinguish between immunity to the disease and resistance to the disease. By immunity we mean the following: If an individual who has never been infected with live virus, is injected with the killed virus (Salk vaccine) he will produce circulating antibodies. He may then be regarded as immune on a subsequent infection by live polio virus through the intestinal tract. He will show no resistance to the disease in the sense that virus will be able to grow in the intestinal mucosa, and this phase of the disease will not be affected by the circulating antibodies. As a result of the infection the titer of the circulating antibodies may be further increased (booster effect) and the circulating antibodies may prevent the spread of the disease through the blood circulation from the intestinal mucosa to the brain.

In contrast to the individual who had never been infected with live polio virus but who has been made immune through vaccination with the killed virus and who, therefore, is immune but does not possess resistance to the disease as explained above, an individual who has been infected with the killed virus has thereby acquired both immunity and resistance to the disease. Upon a subsequent infection with the live virus the intestinal disease is

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Witnessed - January 10,1957

Carol Andrén

resisted in the sense that the virus survives in the intestinal mucosa for a period of time which is much shorter than the survival time of the virus in an individual who is immune but not resistant.

It has been proposed to make individuals resistant to polio virus by first making them immune through the injection of Salk vaccine and subsequently infecting them with the live (attenuated) polio virus. According to this invention the same result can be accomplished by injecting into an individual (who has been previously immunized by means of using the Salk vaccine) a mixture of the killed virus (for instance Salk vaccine) and an excess of antiserum or antibody to the killed virus. The antibody to the killed virus can be obtained by immunizing horses or humans, preferably through repeated injections, with the killed polio virus. From the serum thus obtained from humans or horses the antibody can be concentrated in the customary manner, and the agent for producing resistance to polio myolitis is obtained by mixing the killed polio virus with an excess of the specific antibody. Persons who are made disease resistant by ~~repeated~~ injections of a sufficient dose (or repeated doses) of this agent (to which we shall refer below as DR agent to indicate that it confers disease resistance) will show resistance to polio myolitis in the following sense: if they are infected with live polio virus (of the strain for which the DR agent is specific) they show a much shorter course of the intestinal phase of the disease, i.e. the virus disappears from the intestine much faster than would be the case for persons who have never been infected with the live virus, and may or may not have been immunized by the injection of the killed virus (Salk vaccine).

Witnessed - January 10, 1957.

Carol Andrén

The above example is a special case of a more general principle. There are a number of known diseases where the first phase of the disease consists in the invasion of the intestinal nasal or bronchial mucosa by an infectious agent (such as for instance a virus or a microbe) and this first phase of invasion may or may not be followed by a systematic invasion through the route of the blood circulation (viremia or bacteremia). Many of these diseases confer resistance to the individual for a shorter or longer period of time. During this period of ~~time~~ resistance renewed exposure to the same infectious agent leads to a disease which is milder and of shorter duration. According to this invention such resistance can be conferred on an individual by injecting a mixture of either the killed infectious agent (or else a suitable antigen extracted from the infectious agent) and an excess of antibody which is specific for this infectious agent.

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Witnessed- January 10, 1957. Leo Szilard

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New York, January 10, 1956.

Leo Szilard

Witnessed: January 10, 1957.

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