AN ACCELERATED FEBRILE REACTION IN MONKEYS UPON REINOCULATION WITH POLIOMYELITIS VIRUS*

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The course of poliomyelitic infection in monkeys during the incubation period has recently been made the object of careful study by Kramer, Hendrie and Aycock (1). As the result of these investigations the authors have described a regular and distinct rise in temperature during the preparalytic stage, occurring as a rule 1 or 2 days before the onset of the first clinical symptoms of the disease. This fundamental observation, which incidentally agrees with a similar report of Fairbrother and Hurst (2) is of particular interest inasmuch as it provides a deeper insight into that latent phase of the infection during which the virus grows in the tissues preparatory to the production of lesions.

In the following study we were primarily concerned with the febrile response in monkeys, which had previously been in contact with poliomyelitis virus, upon reinoculation with the same virus. Reasoning by analogy with other infectious processes, we should expect that previous contact with the antigen would leave the reacting susceptible tissue cells in a state of altered receptivity, one phase of which might conveniently be detected through observation of the body temperature. In order to study the various aspects of this problem we have traced the temperature curves, after reinoculation, in monkeys which were in various stages of convalescence from a preceding poliomyelitic infection and in monkeys which had received a number of injections of live virus by various routes of administration in an attempt at active immunization (3).

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Febrile Reaction upon Reinoculation in Recovered Monkeys

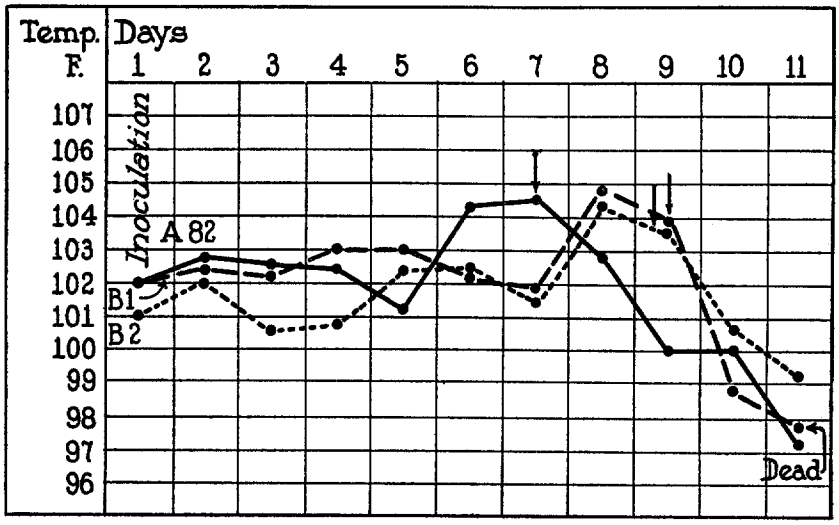
In the first series of experiments three recovered monkeys (52, 36 and 40) were reinoculated by cerebral injection with the same strain of virus* (1 cc. of a 10 per cent cord emulsion); one normal monkey (B2) being infected at the same time for purpose of control. All three convalescent monkeys had recovered from a moderately severe attack of poliomyelitis 5 to 18 months previously, and still showed at the time of the experiment definite residual paralysis of the legs or arms. Needless to say, none of the recovered monkeys gave any evidence of a renewed attack of the disease during a period of observation of 6 weeks, while the control animal came down with typical poliomyelitis on the 9th day after inoculation. The control animal, in accordance with the observations of Kramer, Hendrie and Aycock, exhibited the characteristic febrile reaction the day before the clinical onset of the disease. The temperature curves† of the three recovered monkeys, on the other hand, showed a fairly well marked rise 24 hours after inoculation, followed by a rather sharp subsequent drop before normal values were reattained. (Graphs 1 and 2.)

In order to evaluate the significance of the transitory initial rise of temperature in the recovered monkeys, particularly so as to avoid confusion with the somewhat similar early traumatic reaction in the control, we have, in a second series of experiments, analyzed the febrile reaction during the first 48 hours after inoculation by taking several daily readings at frequent intervals. Thus, another group of four recovered monkeys was reinoculated by intracerebral injection, the experiment being controlled by simultaneous inoculation of two normal monkeys (B9 and B8). In two of the recovered monkeys (A18 and A91) the onset of the previous infection dated back 3 and 6 months, respectively, while the remaining two convalescents (A70 and A95) had barely recovered from a very recent attack of the disease

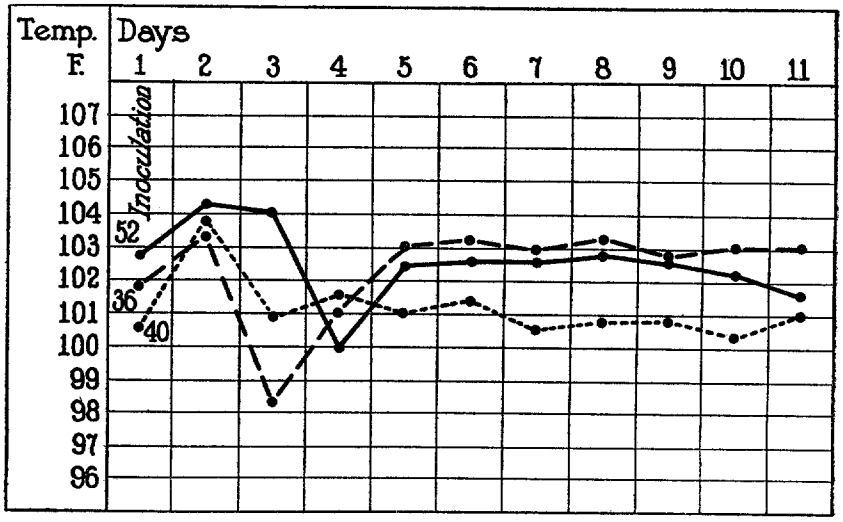
* The virus used in this work was a strain isolated by Dr. Aycock.

† The temperature curves were compiled from daily rectal measurements taken during the incubation period. Before taking the temperature, the monkeys should be subjected to as little physical exertion as possible. The same certified thermometer was used throughout this work. All readings are noon temperatures (3 minutes) unless otherwise indicated. Whenever an animal died, a careful autopsy was made to rule out any possible enteric infection or tuberculosis.

(2 to 3 weeks before). The temperature curves (Graph 3) demonstrate three different types of febrile reaction in those six animals, each type characteristic for each group of monkeys. While both of the

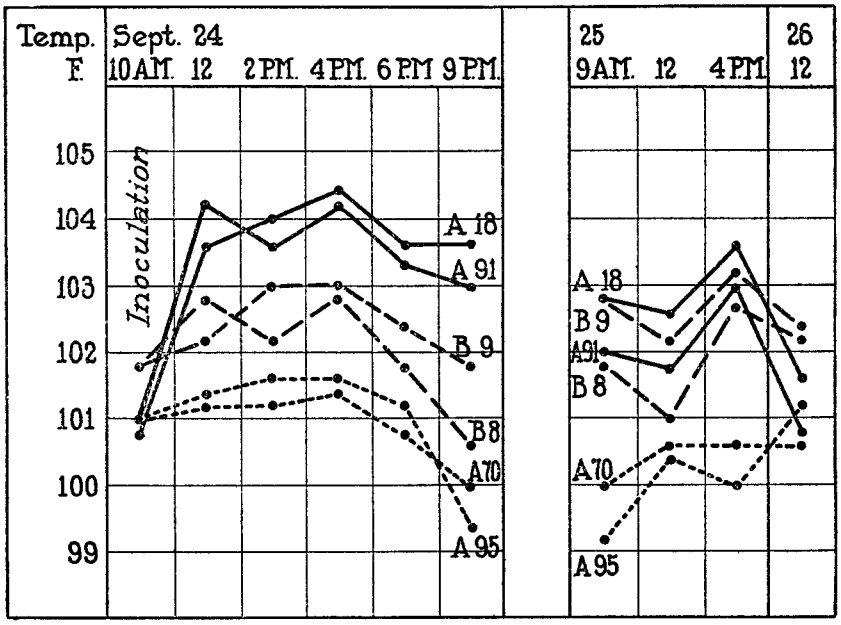


GRAPH 1. Primary infection in three control monkeys (A82, B1 and B2). The arrows indicate the onset of symptoms.



GRAPH 2. Reinoculation of three recovered monkeys (52, 36 and 40).

"old convalescents" responded within the first 2 hours after inoculation with a high and sustained rise of the temperature, the body temperature of the two "recent convalescents" showed no more fluctuation than is common for the daily physiological oscillation. In contrast herewith, the temperature in the two controls reached intermediate values such as have been reported before by Kramer, Hendrie and Aycock.



GRAPH 3. Comparison of febrile reaction during the first 48 hours after reinoculation in recovered monkeys with febrile reaction of primary infection.

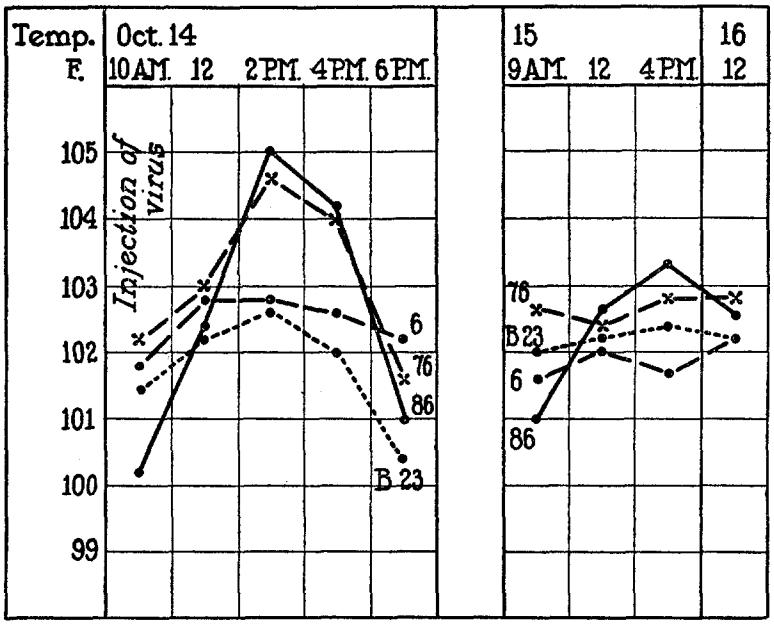
———— Old convalescents (A18, A91).

— — — Normal controls (B9, B8).

------- Recent convalescents (A70, A95).

In the further course of this work we were interested in investigating whether killed virus was capable of eliciting a febrile response in recovered monkeys, comparable to that following reinoculation with live virus. At the same time it became important to ascertain how the reaction would proceed, if the antigen was introduced by the subcutaneous route, a method which circumvented the acute inflammatory reaction incidental to intracerebral inoculation. Accordingly,

two recovered monkeys, both of which gave a history of a mild attack of poliomyelitis several months before, were injected with killed virus (10 per cent virus cord suspension, heated for ½ hour at 65°C.), the one animal (86) receiving 1 cc. of the supernatant intracerebrally, the other (76) 1.5 cc. by subcutaneous injection. For purpose of control a third recovered monkey (6) was inoculated intracerebrally



GRAPH 4. Febrile reaction during the first 48 hours after injection of killed virus in recovered monkeys.

———Recovered monkey injected intracerebrally with killed virus (86).

—x—x—Recovered monkey injected subcutaneously with killed virus (76).

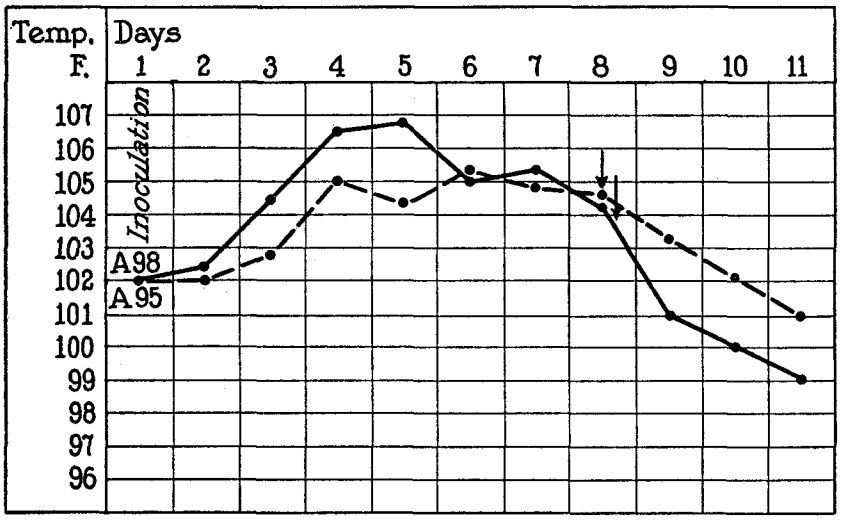
— — — Recovered monkey injected intracerebrally with normal monkey cord emulsion (6).

- - - - - - - Normal monkey injected intracerebrally with live virus (B 23).

with 1 cc. of the supernatant of a 10 per cent suspension of normal monkey cord, a fourth normal monkey (B23), infected with live virus intracerebrally, completing the experimental series. The temperature curves of the four animals, as recorded in Graph 4, demonstrate again an immediate and sharp rise of the temperature after intracerebral injection and a less prompt though distinct febrile reaction following

subcutaneous injection of killed virus in two of the recovered monkeys (86, 76), while the temperature of the two control animals (6, B23) remained within physiological limits during the period of observation (72 hours).

In repeating the fundamental experiments described above, either with the same arrangement or under slightly differing conditions, essentially identical results were obtained in each instance, although the intensity of the febrile reaction as to promptness and magnitude has naturally shown some variation from animal to animal. It seems only logical to assume that recovery from the disease, even at the same fixed time after infection, leaves no two individuals in exactly the same state of immunity.

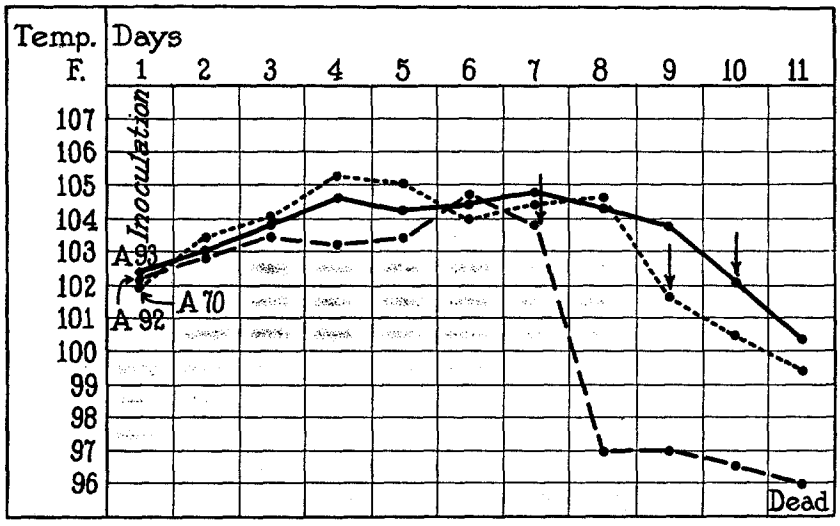


GRAPH 5. Inoculation of two sensitized monkeys (A98 and A95). The arrows indicate the onset of symptoms.

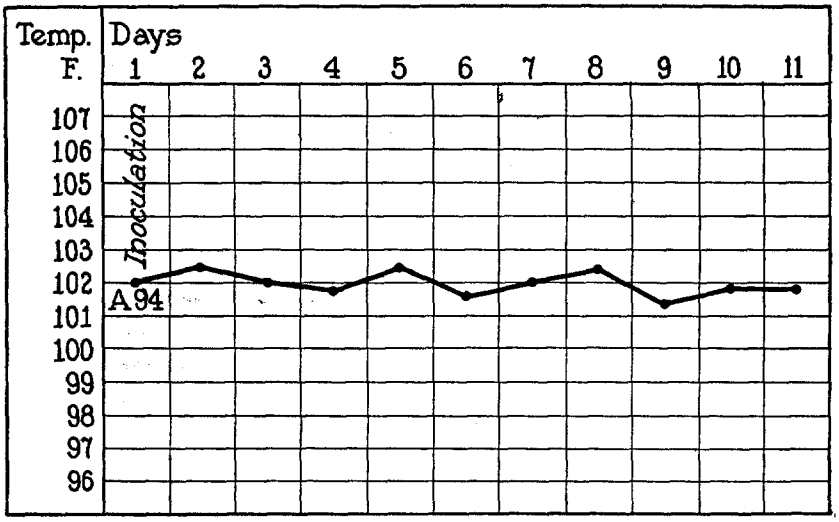
Febrile Reaction upon Inoculation in Sensitized Monkeys

Inasmuch as the previous work had shown that recovery from poliomyelitic infection is associated with an altered response of the convalescent animal towards reintroduction of the same antigen, it became of interest to ascertain whether a similar allergic reaction could be demonstrated upon reinoculation of monkeys, in which artificial immunization by treatment with subinfective doses of virus had been attempted. To study this phase of the problem, six monkeys

were available, all of which had received a number of injections of live virus by different routes (subcutaneous, intraperitoneal, intrarectal)



GRAPH 6. Inoculation of three sensitized monkeys (A93, A92 and A70). The arrows indicate the onset of symptoms.



GRAPH 7. Temperature curve of sensitized monkey after intracerebral injection of normal monkey cord (A94).

over a period of 6 weeks (3). Five of these (A70, A92, A93, A95, A98), after a free interval of approximately one month, were inoculated by cerebral inoculation with the same strain of virus, together with one normal control (A82), the sixth immunized animal (A94) receiving an intracerebral injection of normal monkey cord instead. All monkeys inoculated with the virus came down promptly, from 7 to 10 days later, with typical poliomyelitis, the severity of the disease in the treated group hardly differing from that of the control. Inspection of the temperature curves, however (Graphs 1, 5 and 6), reveals an entirely different response of the treated animals to inoculation as compared with the febrile reaction of the primary infection in the control monkey. While the latter went through the typical febrile reaction,—the temperature remaining practically normal during the entire incubation period except for an abrupt rise 24 or 48 hours before the development of objective clinical symptoms,—the temperature curves in four of the five treated animals showed a precocious elevation on the 3rd or 4th day after inoculation with a high plateau during the remainder of the incubation period. The injection of normal cord in the sixth treated animal did not affect the normal body temperature (Graph 7).

DISCUSSION

The observations recorded in this paper are of interest inasmuch as they remind one forcibly of the accelerated febrile reactions observed with allergic phenomena in general, such as the pyrogenic reaction of Friedberger's in classical anaphylaxis, the syndrome of serum sickness, the tuberculin reaction and, finally, vaccinial allergy (v. Pirquet, Force and others). In each of the instances quoted antigenic substances, which in the normal animal produce either no effect at all or lead to a train of pathological symptoms only after a definite and fixed incubation period, cause an accelerated reaction upon reintroduction into a specifically sensitized individual. The obvious parallelism between such allergic reactions and the accelerated febrile response to poliomyelitic reinoculation in monkeys which had previously been in contact with the virus, suggests that sensitization in poliomyelitis may be of frequent occurrence. As a matter of fact, several authors have entertained this viewpoint before, without however

being able to adduce convincing experimental evidence for its support (Roemer (4), Shaughnessy, Harmon and Gordon (5)).

There can hardly be any doubt but that the accelerated febrile reactions observed by us under various circumstances were due to specific factors. This is proven not only by the absence of any reaction after intracerebral injection of normal monkey cord into recovered or sensitized monkeys, but more particularly supported by the fact that the type of sensitization apparently is determined by special conditions of tissue susceptibility. Thus we find monkeys shortly after an attack of poliomyelitis completely anergic to reinoculation with virus. As the interval increases, the febrile response of the recovered animal is an almost immediate one and of marked intensity, though of short duration. In either instance the animals enjoy complete protection against another attack of the disease. On the other hand, monkeys which have received a number of subcutaneous or intraperitoneal injections of live virus respond, on the average, 3 or 4 days after cerebral inoculation with a sharp and prolonged rise of the temperature, in the majority of the cases eventually succumbing to the infection in spite of the attempted immunization. In primary infection, finally, the disease runs practically an afebrile course during the entire incubation period,—except for a slight, transitory traumatic reaction on the day or the day after the infection, —until 24 or 48 hours before the onset of clinical symptoms, when a critical rise of the temperature occurs.* Thus, there appears to exist a close correlation between the different degrees of increased or decreased susceptibility and the type of febrile reaction. It is quite possible, that the allergic fever reaction could be used as an index for susceptibility in the human, provided that current interpretation of the insusceptibility of the older age groups on the basis of a latent immunization by repeated contact with subinfective doses of virus is in accordance with the actual facts. The possibility of using killed virus subcutaneously for this purpose would render such a test practicable. Further experiments will have to elucidate the relation between allergy and circulating viruscidal antibodies.

* While in most cases the temperature curves of primary infection have conformed with this type of febrile reaction, we have occasionally observed a more gradual development of the fever during the latter third of the incubation period, particularly in the milder and subacute cases.

If sensitization to the virus occurs as readily as our data would seem to indicate, the observations made in this paper may also furnish a possible explanation for the difficulties commonly encountered in obtaining protection with any degree of regularity against the disease in monkeys by the ordinary methods of active immunization (3). Even intracerebral inoculation with a subinfective dose of virus, according to Amoss (6), instead of conveying immunity to the monkey, tends to render the animal more susceptible to a repeated inoculation. Of particular interest in this connection is the fact that the highest immunity index was obtained by Aycock and Kagan (7) with prolonged intradermal immunization, a procedure which carries the essential characteristics of a desensitization process. But even this method rarely insures protection against more than one subsequent test infection, the immunized animals frequently succumbing to repeated inoculation. This observation, which otherwise is wholly incompatible with the conception of solid immunity in virus diseases, may readily be explained on an allergic basis.

The described accelerated febrile reaction appears to be, at present, the only demonstrable indication for the participation of allergic factors in the immunity against poliomyelitis, since we have been repeatedly unsuccessful in eliciting any local hyperergic reaction in convalescent or immunized monkeys in which the virus was either injected intradermally or instilled into the conjunctival sac.

SUMMARY AND CONCLUSIONS

1. Primary poliomyelitic infection in the monkey, as a rule, is characterized by no significant increase in the body temperature during the incubation period until 48 or 24 hours before the onset of clinical symptoms, when a critical rise of the temperature occurs.

2. The temperature curve of recovered monkeys on intracerebral reinoculation shows an almost immediate and marked febrile reaction during the first 24 or 48 hours after inoculation. A similar accelerated febrile reaction may be obtained in recovered animals after subcutaneous injection of killed virus. In case the previous infection is of very recent date, reinoculation may lead to no demonstrable reaction whatsoever.

3. Monkeys, which have received a number of parenteral injections of live virus, respond to intracerebral infection with a precocious and prolonged febrile reaction on the 3rd or 4th day after infection which may last until the onset of symptoms.

4. The altered response to reinoculation of monkeys which have previously been in contact with the virus, suggests a close analogy with the accelerated reactions observed in allergic phenomena.

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