THE ACTION OF CORTISONE ACETATE ON CELL-MEDIATED IMMUNITY TO INFECTION

SUPPRESSION OF HOST CELL PROLIFERATION AND ALTERATION OF CELLULAR COMPOSITION OF INFECTIVE FOCI*

By ROBERT J. NORTH, Ph.D.

(From the Trudeau Institute, Saranac Lake, New York 12983)

(Received for publication 23 July 1971)

Corticosteroids in sufficient doses are known to reduce the immigration of leukocytes into sites of inflammation (1-3), to cause a pronounced depletion of lymphocytes in lymphoid tissue (4), and to suppress immune responses leading to antibody production and homograft rejection (5-7). In view of this knowledge, it is not surprising that these compounds can suppress host resistance to a wide range of bacterial infections (1). It was anticipated, therefore, that they should also suppress the development of cell-mediated immunity to infection with *Listeria monocytogenes*. It is known that immunity to this facultative intracellular parasite is expressed by activated macrophages (8), but is mediated by a population of immunologically committed lymphocytes (9). It is also known that the development of anti-*Listeria* immunity is associated with occurrence of several highly predictable events in the host. For instance, there is a massive division of lymphoid cells in the spleen (10), a wave of vigorous proliferation on the part of resident macrophages in the liver and peritoneal cavity (10, 11), and an accumulation of monocyte-derived macrophages at infective foci in the tissues (12). It is logical to postulate that the first-mentioned event represents the production of the immunologically committed lymphocytes, while the other events represent the mobilization of effector macrophages (12, 13). This communication will describe the effect of cortisone acetate on these major components of the host response.

**Materials and Methods**

*Animals.*—Specific pathogen-free adult male mice weighing between 18-20 g each were employed. The colony was obtained from Charles River Breeding Laboratories, North Wilmington, Mass., and was maintained in an infection-free environment and fed on a sterile vitamin-enriched diet.

*Bacteria.*—*Listeria monocytogenes* (strain EGD) was maintained in a virulent state by re-

*This work was supported by grant No. AI-07015 from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Department of Health, Education, and Welfare.
peated passage in mice. It has an ID₉₀ of 5 × 10³ when injected intravenously. Before each experiment it was isolated from the spleen, grown in Trypticase soy broth (Baltimore Biological Laboratories, Baltimore, Md.) for 18 hr, and washed and diluted appropriately in 0.9% sodium chloride solution. All infections were initiated by injecting 10⁴-2 × 10⁴ organisms intravenously. The numbers of *L. monocytogenes* in the livers and spleens were enumerated by plating out serial dilutions of organ homogenates on nutrient agar. Five mice were used for each time point studied.

*Estimating Host Cell Proliferation.*—Changes in the numbers of cells proliferating in the livers and spleens during infection were detected by pulse labeling with tritiated thymidine TdR-³H. At each time point indicated, five mice were injected intravenously with 20 μCi of TdR-³H (3 Ci/m mole) dissolved in 0.9% sodium chloride solution. 30 min later their livers and spleens were weighed and a portion extracted for DNA as described previously (11). DNA-³H was counted in a Beckman LS-100 liquid scintillation counter (Beckman Instruments, Inc., Fullerton, Calif.).

*Radioautography.*—Another portion of the livers and spleens were fixed in 10% formalin and embedded in glycol methacrylate (14). Radioautography on sections of 2 μ thickness was performed with Ilford K5 liquid emulsion (Ilford Ltd., Ilford, England) (15). After 2 or 3 wk exposure, the preparations were processed (15) and stained with methyl green-pyronin (14).

*Cortisone Acetate.*—Cortisone acetate (Merck and Co., Inc., Rahway, N.J.) was thoroughly suspended and diluted in 0.9% sodium chloride solution. In all cases it was administered subcutaneously in a volume of 0.2 ml.

**RESULTS**

(a) **Effect of Cortisone Acetate on Growth of Listeria in the Liver and Spleen.**—

*Minimum effective dose:*

Preliminary experiments showed that the development of immunity to infection with *L. monocytogenes* is completely inhibited by a single 10 mg dose of cortisone acetate given at the beginning of infection. In order to determine the minimum dose required to give the same effect, mice were injected with 0.5, 1.0, 2.5, 5.0, or 10 mg of cortisone 1 hr after initiating infection with a standard dose of organisms. The results in Fig. 1 show that a dose of 2.5 mg or more completely inhibits the development of immunity as evidenced by unrestricted growth of the parasite in the liver or spleen. It will be noted that a dose of 1 mg causes only a delay in the acquisition of immunity, while 0.5 mg is without significant effect. Therefore, 2.5 mg was taken as the minimum lethal dose for infected mice.

*Effect on different phases of the host response:* The growth curve of *L. monocytogenes* in the liver and spleen can be separated into three stages: an initial stage of active growth, a stage of reduced growth, and a period of progressive bacterial elimination. It is obvious that the onset of bacterial elimination in the liver and spleen represents the expression of acquired antibacterial immunity by activated macrophages (8). The effect of cortisone acetate on these different stages of the bacterial growth curve is shown in Fig. 2. It can be seen that a single dose (2.5 mg) given at any time during the first 3 days results in the immediate resumption of unrestricted bacterial multiplication which continues

---

1 Abbreviation used in this paper: TdR-³H, tritiated thymidine.
until the death of the hosts. The effect is less striking by the 4th day, particularly in the spleen where suppression of the immune response is only transient. The effect is even less striking at later times (results not included) when higher

levels of antimicrobial immunity have been established. This is best illustrated by the results of experiments in which 10-day-infected mice were challenged intravenously with a large (10^9) dose of homologous organisms. The results shown in Fig. 3 reveal that the expression of acquired antimicrobial immunity by convalescing mice is only slightly suppressed by 2.5 mg of cortisone acetate

![Diagram](image-url)
given at the time of challenge. It should be pointed out that there are less than 100 organisms in the livers and spleens of 10-day-infected mice, and that these small numbers could be ignored when estimating the much larger numbers of organisms resulting from the challenge infection. The results of these experiments show, therefore, that while the developmental stage of immunity is highly sensitive to cortisone acetate, established immunity becomes increasingly less susceptible.

**Fig. 2.** Effect of 2.5 mg of cortisone acetate when given at different stages of infection. A dose given at any time during the first 3 days results in a resumption of unrestricted bacterial multiplication. The drug had progressively less effect from the 3rd day on.

**Effect when given before infection:** The possibility that the induction of the development of anti-*Listeria* immunity is dependent on the existence in the normal animal of a population of cortisone-sensitive cells was tested by injecting mice with 2.5 mg of cortisone acetate at 72, 48, or 24 hr before infection. The results in Fig. 4 show that the development of immunity is severely suppressed by an injection of the drug given 24 hr before infection. It is obvious, however, that the effect of the drug wanes rapidly after 24 hr in that mice treated 48 hr
before infection are able to develop appreciable levels of immunity within a further 48 hr, while those treated 72 hr before infection are quite unaffected by cortisone. It will be noted that only the liver growth curves are presented. This is because cortisone acetate causes a large decrease in the size of the spleen, and a much reduced initial uptake of the bacterial inoculum. In terms of rates of multiplication, however, the growth curves in both organs were found to be comparable.

![Graph showing effect of cortisone acetate on liver and spleen growth curves](image)

Fig. 3. Effect of 2.5 mg of cortisone acetate on established immunity of 10-day-infected mice. Normal mice, 10-day-infected mice (IMM), and 10-day-infected mice treated with cortisone acetate (IMM CORT) were challenged with approximately $10^5$ L. monocytogenes. It can be seen that cortisone acetate does not greatly affect established immunity.

(b) Effect of Cortisone Acetate on Cellular Components of the Host Response.—It was shown in the preceding section that a single 2.5 mg dose of cortisone acetate given at the beginning of infection completely suppresses the development of acquired antimicrobial immunity. The following experiments were performed in order to determine whether this suppression of immunity can be explained in terms of the action of cortisone acetate on known cellular parameters of the host response.
**Effect on splenic lymphoid cell proliferation:** It has been shown previously (10) that infection with *L. monocytogenes* results in a striking increase in the division of pyroninophilic cells in the splenic red pulp. It has also been shown by cell transfer experiments (9) that the spleens of such animals progressively acquire a large population of immunologically committed lymphocytes over the first 6 days of infection. It would seem logical to postulate, therefore, that increased spleen cell proliferation represents the production of committed lymphocytes.

**Fig. 4.** Effect of 2.5 mg of cortisone acetate when given before infection at the times indicated. The development of immunity is not suppressed when the drug is given 72 hr before infection, but significant suppression is seen when it is given 24 hr before infection.

It was anticipated, in view of the known susceptibility of lymphoid cells to corticosteroids, that splenic lymphoid cell proliferation would be suppressed by cortisone acetate. Fig. 5 shows the effect on cellular proliferation in the spleen of 1.0, 2.5, or 5 mg of cortisone acetate given 1 hr after initiating infection. It will be seen that *Listeria* infection normally results in a striking and progressive increase in spleen cell proliferation over the first 5 days of infection as measured by TdR-\(^3\)H incorporation into total DNA. In contrast, cortisone acetate in all doses causes a pronounced suppression of cell proliferation as evidenced by an initial fall in TdR-\(^3\)H incorporation over the first 48 hr of
infection. This initial fall is followed, however, by a rebound in TdR-3H incorporation, the intensity of which depends on the dose of cortisone acetate injected. In the case of those animals which received 2.5 or 5.0 mg, the rebound comes too late to enable spleen cell proliferation to catch up to control values before mice begin dying on the 4th day. In the case of the 1.0 mg dose, which is known only to delay the development of immunity, the rebound is fast enough to bring proliferation close to control values by the 3rd day. The results show,
therefore, that those doses of cortisone acetate that completely suppress immunity also severely depress and delay infection-induced spleen cell proliferation.

![Diagram showing the effect of cortisone acetate on Kupffer cell division in liver sinusoids during infection.](image)

**Fig. 6.** Effect of 1.0, 2.5, and 5.0 mg of cortisone acetate on the division of Kupffer cells in liver sinusoids during infection as measured by TdR-\(^{3}H\) incorporation into liver DNA. Infection normally results in substantial division which peaks on days 2 or 3. Cortisone acetate greatly delays this component of the response.

It is important to emphasize that cortisone, in all doses, causes a temporary reduction in spleen weight. The observed effects of cortisone on the rates of TdR-\(^{3}H\) incorporation could be explained, therefore, in terms of its ability to reduce the total number of available cells that could be induced to divide in
response to infection, rather than in terms of an effect on the per cent of responding cells or their individual rates of DNA synthesis. In fact, if TdR-3H incorporation values are expressed in terms of counts per unit weight of spleen, significant rebounds in TdR-3H incorporation occur 24 hr earlier than indicated in Fig. 5. Thus, there is an increase in the proportion of replicating cells at these times even though their total numbers remain greatly reduced.

Concurrent experiments showed that cortisone acetate also causes a reduction in TdR-3H incorporation in the spleens of normal mice. As with infected mice, this reduction is associated with a loss in spleen weight over 48 hr and is followed by a rebound. The rebound, however, does not exceed the TdR-3H incorporation values of normal spleens.

Effect on proliferation of fixed phagocytes in the liver: It is known (11) that infection with L. monocytogenes results in a marked increase in the replication of fixed phagocytes in liver sinusoids. The effect of cortisone acetate on this component of the host response is shown in Fig. 6, where it can be seen that infection normally results in a large increase in TdR-3H incorporation into liver DNA over the first 3 days of infection. This has been shown already to correspond to a progressive increase in the numbers of labeled phagocytes in liver sinusoids (11). The effect of cortisone acetate in all doses was to cause a substantial delay in the onset of this increased cell division. In those mice given 2.5 or 5 mg, and which consequently succumb to infection, the onset of liver macrophage division is delayed for about 48 hr. The 1.0 mg dose, however, results in only a 24 hr delay, so that substantial cell division occurs at 48 hr of infection and approaches control values by the 3rd day. It will be noted that the incorporation values for mice given 2.5 and 5 mg of cortisone acetate are only shown for the first 3 days because the mice began dying on the 4th day. Their livers became so heavily infected by this time that incorporation values were rendered meaningless.

Concurrent experiments with normal mice showed that the doses of cortisone acetate used do not result in increased TdR-3H incorporation into normal liver during the time interval of the experiment. It is apparent, therefore, that the delayed increases in incorporation described above were because of infection. Radioautography of the above material showed, in all cases, that increased incorporation was almost entirely because of an increase in the number of labeled cells at the margins of liver sinusoids.

Effect on cellular events at infective foci in the liver: Histology shows that multiplication of L. monocytogenes occurs mostly within infective foci. It is obvious, therefore, that acquired antimicrobial immunity must be expressed predominantly at these sites. Evidence consistent with this view resulted from experiments which showed (12) that the expression of anti-Listeria immunity in the liver is coincident with a massive accumulation of monocyte-derived macrophages at infective foci. It is almost certain, therefore, that it is this
population of macrophages which expresses immunity. The following experiments were performed in order to investigate the effect of cortisone acetate, given at the time of initiating infection, on the accumulation of these cells at infective foci.

Mice were injected with 10 μCi of TdR-3H 2 and 1 hr before infecting with a standard dose of organisms. This was done to label the dividing precursors of blood monocytes in bone marrow (12). 1 hr later the mice were injected with cortisone acetate, and the effect of the drug on the subsequent entry and accumulation of labeled cells in the liver was measured by radiometry and radioautography. It can be seen in Fig. 7 that labeled DNA normally accumulates in the liver between 24 and 96 hr of infection. Radioautography (Fig. 8) shows, in agreement with previous studies (12), that this accumulation of label is almost entirely because of an accumulation of labeled macrophages at infective foci, so that by 96 hr these cells have almost completely replaced the polymorphonuclear leukocytes which characteristically dominate infective foci during the first 48 hr (9, 12). The effect of cortisone acetate is to cause a substantial delay in the accumulation of labeled DNA into infected livers. This delay lasts for about 24 hr in mice which received 1 mg of the drug, and for about 48 hr in mice which received 2.5 or 5.0 mg. The delays are followed in each case, however, by a striking increase in DNA-3H accumulation which greatly exceeded DNA-3H accumulation in control livers both in rate and extent. It was evident that this enhanced influx and accumulation of label either represented increased numbers of labeled macrophages, or was because of the entry of a different type of labeled cell. Radioautography shows that the bulk of the increased label is because of an accumulation of large numbers of labeled polymorphonuclear leukocytes at infective foci (Fig. 8). In contrast, labeled macrophages were relatively few in number in infective foci of mice which received 1.0 mg of cortisone acetate, and were even less numerous in mice which received larger doses of the drug. It is evident, therefore, that cortisone acetate does not reduce the migration of polymorphs into infective foci. Polymorphs labeled in bone marrow by a pulse of TdR-3H before infection are thus able to enter infective foci at a time when their accumulation normally ceases, and their place is taken by immigrant macrophages.

The sustained immigration of polymorphs was not the only feature of infective foci in cortisone-treated mice. It was observed, in addition, that those polymorphs which initially enter infective foci apparently do not become effete and disintegrate as they normally do in infective foci in control mice. The very large numbers of polymorphs observed in lesions on the 3rd day was, therefore, not only because of their sustained migration into infective foci, but apparently also because of an extension of their life-span at these sites.

It is difficult to judge the contribution of labeled monocytes to lesions so
Fig. 7. Effect of 1.0, 2.5, and 5.0 mg cortisone acetate on the influx and accumulation of labeled cells in the liver. All mice were injected intravenously with 10 μCi of TdR-3H 1 and 2 hr before infection to labeling the dividing precursors of monocytes in bone marrow. Cortisone was given 1 hr after initiating infection. Infection normally leads to an influx and accumulation of labeled monocytes into lesions and sinusoids after day 2 of infection. This influx was delayed by cortisone acetate, but the delay was followed by a larger than normal influx of DNA-3H which was found to correspond to the accumulation of large numbers of labeled polymorphs in lesions. The results are expressed as radioactive counts above normal control values.

heavily populated with polymorphs. It appeared, however, that labeled macrophages eventually reach normal numbers in lesions of mice receiving 1.0 mg or less of cortisone acetate, but are much less numerous in the lesions of mice receiving lethal doses of the drug.
FIG. 8. Radioautographs of infective foci in the livers of normal mice (a, b) and cortisone-treated mice (c, d) on day 3 of infection. In control mice infective foci are being populated by macrophages, some of the precursors of which were labeled with TdR-³H before infection. In contrast, the lesions of cortisone-treated mice are populated by large numbers of polymorphs the precursors of which were also labeled before infection. (a) X 440; (b) X 1080; (c) X 440; (d) X 1080.
DISCUSSION

It has been shown (12) that acquired anti-Listeria immunity is expressed at a time when cells with the labeling characteristics of blood monocytes accumulate at infective foci in the tissues. The present study shows that a single injection of cortisone acetate given 1 hr after initiating infection greatly delays and suppresses this component of the host response. It is apparent, therefore, that the suppression of immunity by cortisone acetate is ultimately because of its ability to cause a failure of effector macrophages to migrate in adequate numbers to sites of bacterial implantation. Thus, cortisone acetate may either block the production of blood monocytes in bone marrow, or affect their fate after they enter the circulation. In favor of the first proposition, it has been shown by others (16) that relatively large doses of corticosteroids cause a rapid reduction in the number of monocytes in circulation. Preliminary experiments in this laboratory show, however, that the small doses of corticosteroids employed in the present experiments do not affect the numbers of labeled monocytes migrating into sterile peritoneal exudates in normal mice. It would seem unlikely, therefore, that cortisone owes its infection-enhancing effects in this model to an effect on monocyte production in bone marrow, or impairment of their delivery to tissues. Furthermore, the labeling of the dividing precursors of monocytes in the present study took place before cortisone acetate was injected. It is also unlikely that cortisone acetate greatly impairs the bactericidal activity of macrophages, as evidenced by the finding that the tissues of 10-day-infected mice were still able to inactivate a very large challenge infection with L. monocytogenes after cortisone treatment. The normality of phagocyte function in cortisone-treated animals is attested by published reports which show that the phagocytic and bactericidal activity of polymorphs (17-19), and the phagocytic activity of macrophages (20, 21) are not suppressed by corticosteroids. It seems reasonable to propose, therefore, that cortisone acetate has no important direct effect on the functional activity of monocytes. Its effect on the buildup of these cells at infective foci must, therefore, be exerted indirectly.

Since an infusion of immune lymphoid cells from Listeria-immune donors into normal recipients is known to result in the adoptive transfer of high levels of anti-Listeria immunity (9), it is apparent that the infused lymphoid cells must mediate changes which enable the recipients' own macrophages to express immunity. In fact, experiments still in progress (Mackaness and North; Truitt and Mackaness) have shown that the rapid onset of the expression of adoptive immunity in such recipients is associated with a much faster than normal accumulation of monocytes at sites of bacterial implantation. It is apparent, therefore, that immunologically committed lymphocytes are in some way involved in mediating the cellular events at infective foci. This argument is supported, for instance, by the published findings (22, 23) that granuloma
formation in Schistosomiasis is greatly accelerated in animals which have first been rendered hypersensitive to schistosome antigens. This type of granuloma formation thus appears to be under the influence of specific cellular mediators. It seems reasonable to postulate, therefore, that the failure of monocytes to accumulate at infective foci in cortisone-treated mice is primarily because of a suppression of the lymphoid component of the response. The severe suppression of splenic lymphoid cell proliferation observed in cortisone-treated mice is consistent with the view that the drug interferes with the formation of immunologically-committed lymphocytes. Direct evidence to support this hypothesis will appear in a forthcoming publication.  

The reason for the sustained immigration of polymorphs to infective foci in cortisone-treated mice is still under investigation. Presumably it represents an attempt by the host to make up for a deficit of macrophages in the face of unrestricted bacterial multiplication at these sites. Since, however, the parasite multiplies unhindered in polymorph lesions, it seems that this cell type has little part to play in resistance to the infectious agent. The enhanced polymorph accumulation at infective foci in cortisone-treated mice is reminiscent of the accumulation of polymorphs which occurs at the expense of macrophage accumulation in delayed skin reactions of tuberculin-sensitive rabbits treated with cortisone (24). Cortisone treatment does not result in an enhanced polymorph immigration in skin reactions elicited by other means. It is possible, therefore, that a cortisone-induced polymorph accumulation is peculiar to delayed-hypersensitivity reactions elicited either by an injection of soluble antigen into the skin or by the implantation of intracellular parasites in internal tissues.

The suppression of infection-induced Kupffer cell division by cortisone acetate probably does not significantly contribute to the reduced capacity of the host to express immunity. It has already been shown (12) that suppression of Kupffer cell division by local X-irradiation of the liver does not reduce the capacity of this organ to express immunity against minimal Listeria infections. It is possible, however, that division of these cells is important, for the expression of immunity to more severe Listeria infections and other infections. Whether cortisone acetate acts directly on Kupffer cells to inhibit their division has yet to be determined.

SUMMARY

Pulse labeling with tritiated thymidine shows that the response in the mouse to infection with L. monocytogenes includes a large increase in the division of lymphoid cells in the spleen, an increase in the division of macrophages in the liver, and an accumulation of monocyte-derived macrophages at infective foci in the tissues. A single 2.5 mg dose of cortisone acetate given at the beginning

---

2 North, R. J. 1971. The action of cortisone acetate on cell-mediated immunity to infection: selective elimination of committed lymphocytes. Submitted for publication.
of infection greatly delays and suppresses these three components of the host response. The unrestricted bacterial multiplication which follows cortisone treatment is ultimately because of a failure of monocyte-derived macrophages to accumulate at infective foci where they normally express immunity. The accumulation of polymorphs at these sites, in contrast, is enhanced. It is argued that cortisone acetate prevents the accumulation of monocytes at infective foci indirectly by suppressing the production in the spleen of immunologically-committed lymphocytes which are needed to mediate the cellular events at infective foci.

I wish to thank Mr. Jon Deissler and Mrs. Sandra Warner for expert assistance.

BIBLIOGRAPHY

1. Germuth, F. G. 1956. The role of adrenocortical steroids in infection, immunity and hypersensitivity. Pharmacol. Rev. 8:1.
2. Fruham, G. J. 1964. Extravascular mobilization of neutrophils. Ann. N.Y. Acad. Sci. 113:968.
3. Rebuck, J. W., and R. C. Mellinger. 1953. Interruption by topical cortisone of leukocytic cycles in acute inflammation. Ann. N.Y. Acad. Sci. 56:715.
4. Dougherty, T. F., M. L. Berliner, G. L. Schneebeli, and D. L. Berliner. 1964. Hormonal control of lymphatic structure and function. Ann. N.Y. Acad. Sci. 113:825.
5. Elliott, E. V., and N. R. St. C. Sinclair. 1968. Effect of cortisone acetate on 19S and 7S antibody: a time-course study. Immunology. 15:643.
6. Dukor, D., and F. M. Dietrich. 1968. Characteristic features of immunosuppression by steroids and cytotoxic drugs. Int. Arch. Allergy Appl. Immunol. 34:32.
7. Gabrielsen, A. E., and R. A. Good. 1966. Chemical suppression of adoptive immunity. Advan. Immunol. 6:91.
8. Mackaness, G. B. 1962. Cellular resistance to infection. J. Exp. Med. 116:381.
9. Mackaness, G. B. 1969. The influence of immunologically committed lymphoid cells on macrophage activation in vivo. J. Exp. Med. 129:973.
10. North, R. J. 1969. Cellular kinetics associated with the development of acquired cellular resistance. J. Exp. Med. 130:299.
11. North, R. J. 1969. The mitotic potential of fixed phagocytes in the liver as revealed during the development of cellular immunity. J. Exp. Med. 130:315.
12. North, R. J. 1970. The relative importance of blood monocytes and fixed macrophages to the expression of cell-mediated immunity to infection. J. Exp. Med. 132:521.
13. North, R. J. 1970. Suppression of cell-mediated immunity to infection by an antimitotic drug. J. Exp. Med. 132:535.
14. North, R. J. 1971. Methyl green-pyronin for staining autoradiographs of hydroxyethy methacrylate-embedded lymphoid tissue. Stain Technol. 46:59.
15. Caro, L. G., R. P. Tubergen, and J. A. Kolb. 1962. High resolution autoradiography. I. Methods. J. Cell Biol. 15:173.
16. Thompson, J., and R. van Furth. 1970. The effect of glucocorticosteroids on the kinetics of mononuclear phagocytes. J. Exp. Med. 131:429.
17. Hirsch, J. G., and A. B. Church. 1961. Adrenal steroids and infection: the effect of cortisone administration on polymorphonuclear leukocyte functions and on serum opsonins. *J. Clin. Invest.* 40:794.

18. Cohn, Z. A. 1962. Determinants of infection in the peritoneal cavity. II. Factors influencing the fate of *Staphylococcus aureus* in the mouse. *Yale J. Biol. Med.* 35:29.

19. Allison, F., and M. N. Adcock. 1965. Failure of pretreatment with glucocorticosteroids to modify the phagocytic and bactericidal capacity of human leukocytes for encapsulated type I Pneumococcus. *J. Bacteriol.* 89:1256.

20. Gell, P. G. H., and I. T. Hinde. 1953. Effect of cortisone on macrophage activity in mice. *Brit. J. Exp. Pathol.* 34:273.

21. Lovell, R. H., G. B. D. Scott, B. Hudson, and J. A. Osborne. 1953. The effects of cortisone and adrenocorticotrophic hormone on dispersion of bruises in the skin. *Brit. J. Exp. Pathol.* 34:535.

22. Warren, K. S., E. O. Domingo, and R. B. T. Cowan. 1967. Granuloma formation around Schistosome eggs as a manifestation of delayed hypersensitivity. *Amer. J. Pathol.* 51:735.

23. Warren, K. S., and E. O. Domingo. 1970. Granuloma formation around *Schistosoma mansoni* and *S. japonicum* eggs in unsensitised and sensitised mice: size, rate of development, cellular composition, cross reactivity and rate of egg destruction. *Amer. J. Trop. Med. Hyg.* 19:292.

24. Gell, P. G. H., and I. T. Hinde. 1951. The histology of the tuberculin reaction and its modification by cortisone. *Brit. J. Exp. Pathol.* 32:516.