COMPARATIVE EFFECTS OF CORTICOSTEROIDS ON HOST RESISTANCE TO INFECTION IN RELATION TO CHEMICAL STRUCTURE*

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As reported in a preceding paper (1), injections of hydrocortisone acetate into mice harboring latent corynebacteria (acquired either naturally or experimentally) evoke progressive and fatal corynebacterial pseudotuberculosis. That host resistance to a variety of infectious agents can be decreased by administration of corticoids has been repeatedly documented with regard to both experimental infections and activation of latent diseases (2–7). The early decrease of host resistance following corticoid injection is usually attributed to the suppression of the inflammatory process. In investigating the action of corticoids on phagocytic cells, we have had an opportunity to test the effect of 6α-methylprednisolone, 21 sodium hemisuccinate in vivo and in vitro. Despite the higher antiinflammatory activity of this compound as compared with hydrocortisone acetate, it was surprising that latent corynebacterial infection of mice was not provoked to active disease after injection of 6α-methylprednisolone, 21 sodium hemisuccinate as happened after injection of hydrocortisone acetate.

The present report deals with this preliminary observation. It is shown, furthermore, that according to differences in the chemical structure of the steroids, different effects were observed with respect to host resistance even at the cellular level. These differences showed no correlation with the antiinflammatory properties of the drugs.

Materials and Methods

Mice.—The strains of mice and the sources from which they were obtained were the same as described in an earlier report (1) except for the NCS mice which came from the Pasteur Institute colony and were maintained as reported previously (1, 8). Mice 4–6 wk of age were used for all experiments.

Steroids.—The products tested are listed in Fig. 1. Compound I was obtained from Merck, Sharp and Dohme, Rahway, N. J., and from Roussel Laboratories, Paris. Compound II was obtained from Upjohn Laboratories, Paris. Compound III was obtained from Roussel Laboratories, Paris. Compounds IV–VIII were obtained from Specia, Paris. With the exception of

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Fig. 1. Steroids tested.
compound I, which was in the form of a saline suspension containing 25 mg hydrocortisone per ml, all compounds were obtained in a dry form. After addition of sterile saline, compounds II and VII were dissolved, whereas compounds III, IV, V, VI, VIII were in the form of suspensions in saline. We wish to acknowledge with thanks the cooperation of the commercial firms listed above.

Steroid Injections.—Steroids suspensions or solutions were injected subcutaneously, by means of a sterile syringe and No. 27 gauge needle, into mice in the lower dorsal area, previously shaved and cleaned with iodine.

Evaluation of the Antiinflammatory Activity of Steroids.—In each experiment, mice 4–6 wk of age, of the same weight and sex, were kept in groups of five animals per cage. They were injected in both hind foot-pads with 0.05 ml of turpentine. The average diameter of each foot-pad was measured at 24, 25, 28, 36, and 48 hr. with an instrument having calibrated holes. To ascertain antiinflammatory activity, each group of five mice was injected with a drug (or with saline as control) 24 hr after turpentine injection, and measurements of the foot-pads were recorded at various time intervals.

Bacterial Strains.—The stock laboratory strain of Corynebacterium kutscheri was used as described previously (1). Staphylococcus aureus and Klebsiella pneumoniae, type C, obtained through the courtesy of Dr. R. W. Schaedler, and Listeria monocytogenes (9) were cultured in tryptose broth (Difco Laboratories, Inc., Detroit, Mich.). All strains were used after mice passage.

Injective Dose and Route of Infection.—C. kutscheri, S. aureus, and K. pneumoniae were injected intravenously in 0.2 ml doses containing respectively 0.5–1 × 10^9, 0.8–1.2 × 10^9, and 0.6–1.2 × 10^9 bacteria. L. monocytogenes was injected intraperitoneally after dilution in saline, in doses containing 2–3 × 10^5 bacteria in 0.5 ml volume.

Mouse Peritoneal Cells.—Collection of mouse peritoneal cells was made as described previously (10). Briefly, the peritoneal cavities of 25 g NCS mice were washed with 5 ml of medium 199 containing 2.5% bovine serum albumin and 5 units of heparin per milliliter. Upon withdrawal from the peritoneal cavity, 0.02 ml of this suspension was introduced into a Thoma counting chamber. After 30 min of incubation in a moist chamber at 37°C, the cells were observed with a Leitz Ortholux phase microscope (Heine condenser and P.V. 25/0.50 lens). Pictures were taken with a Leica microattachment and Kodak Panatomic X film.

EXPERIMENTAL RESULTS

Effects of Hydrocortisone Acetate, 6a-Methylprednisolone, 21-Sodium Hemisuccinate, and 9a-Fluoro, 16a-Methylprednisolone Acetate upon Activation of Latent Infection with C. kutscheri in C57Bl/6 Mice.—

When C57Bl/6 mice were injected with compounds I, II, and III of Fig. 1, death from corynebacterial pseudotuberculosis occurred (Table I) only in mice treated with hydrocortisone acetate (I) and 9a-fluoro, 16a-methylprednisolone acetate (III). With compound I, death occurred within 6–13 days and with compound III, in 4–8 days. Autopsy revealed abscesses in the lungs, heart, and kidneys. In contrast, no death occurred in mice injected with 6a-methylprednisolone, 21 sodium hemisuccinate (II), either in 10 or 20 mg doses. These striking differences in the reactivation of latency following the administration of three potent antiinflammatory drugs lead us to consider that these differences were the result either of different solubilities of the product, or of the chemical structure of the steroids.
CORTICOSTEROIDS AND HOST RESISTANCE

The fact that repeated injections of compound II were not followed by re-activation of latency, directed our attention especially to the sodium hemisuccinate in position 21 on the molecule of 6a-methylprednisolone. Accordingly, it was of interest to test 9a-fluoro, 16a-hydroxyprednisolone 16a-, 17a-acetone (compound V, Fig. 1) and the same compound which has the alcoholic hydroxyl in position 21 esterified with succinic acid (compound VI, Fig. 1). For the same reason we tested compound VIII which has two molecules of succinic acid in positions 16 and 21. Compound VII (like compound II, readily soluble in saline) was tested comparatively with compound V, from which it differs only by esterification of alcoholic hydroxyl in position 21 with sodium phosphate.

These compounds were used in order to test (a) their antiinflammatory activity and their effects upon (b) reactivation of latent infection, (c) experimental infection, and (d) the types of peritoneal cells following local inflammation.

**Comparative Evaluation of the Antiinflammatory Activity of Compounds I to VIII.**

The results reported in Figs. 2 a and 2 b represent the average values of five experiments. All the eight products tested are seen to be very potent as

### TABLE 1

_Effect of Corticosteroids I, II, and III upon Activation of Latent C. kutscheri Infection in C57Bl/6 Mice_.

<table>
<thead>
<tr>
<th>Corticoids tested</th>
<th>No. Mice</th>
<th>Day of death after injection*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>(I) Hydrocortisone acetate, 10 mg</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>(II) 6α-methylprednisolone, 21 sodium hemisuccinate, 10 mg</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>(II) 6α-methylprednisolone, 21 sodium hemisuccinate, 20 mg</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>(III) 9α-fluoro, 16α-methylprednisolone acetate, 10 mg</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

*S, sacrificed at 15 days. No gross pathology observed.

* Gross lesions and smears positive for _C. kutscheri_ were observed in all mice that died.
antiinflammatory agents. As early as 4 hr after subcutaneous injection of 10 mg of the steroids, a significant decrease of foot-pad thickness could be observed.

This antiinflammatory activity was most pronounced with 6α-methylprednisolone 21 sodium hemisuccinate (compound II) and 9α-fluoro,16α-

hydroxyprednisolone 16α-,17α-acetonide-21-disodium phosphate (compound VII) during the first 4 hr. It is worthy of note that compounds II and VII are readily soluble, in contrast with other compounds which are injected in the form of suspensions in saline. This greater solubility can explain the apparent earlier antiinflammatory activity of compounds II and VII. Later (12 and 24 hr after the induction of inflammation), there were no significant differences among the products tested. The average decrease of foot-pad thickness 24 hr after corticoid injection was of the order of 20% in comparison with mice injected with saline.

![Graph showing comparative antinflammatory effectiveness of corticoid compounds I to IV.](image-url)
Comparative Effects of Steroids upon Reactivation of Latent Infection.

In Table II are summarized the results of three experiments in which C57Bl/6 mice were injected with 10 mg doses of compounds I through VIII. Mice injected with compounds I, III, IV, V, and VII died from an acute corynebacterial infection. In contrast, mice treated with the same dose of compounds II, VI, and VIII were healthy 1 month after injection, and upon autopsy, no gross lesions of corynebacterial infection were observed. Interestingly, the symptom of “moon facies” appeared only in mice treated with 9α-fluoro,16α-hydroxydexamethasone (compound IV). C57Bl/6 mice injected with 9α-fluoro,16α-hydroxydexamethasone 16α-,17α-acetonide,21 disodium phosphate (compound VII) died from an acute corynebacterial infection, despite the high solubility of this compound.
Comparative Effects of Steroids upon Experimental Infections.—
In Table III are summarized the data concerning the effect of compounds I through VIII upon experimental infection of NCS mice. Again, a striking contrast exists between two groups of compounds; I, III, IV, V, VII versus II, VI, VIII.

### Table II

<table>
<thead>
<tr>
<th>Steroids tested</th>
<th>No. Mice</th>
<th>Death after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>I Hydrocortisone acetate</td>
<td>5</td>
<td>7, 9, 9, 10, 11</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>7, 8, 9, 10, 10</td>
</tr>
<tr>
<td>II 6a-methylprednisolone, 21 sodium hemisuccinate</td>
<td>5</td>
<td>S, S, S, S, S*</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>S, S, S, S, S</td>
</tr>
<tr>
<td>III 9a-fluoro, 16-methylprednisolone acetate</td>
<td>5</td>
<td>4, 5, 4, 6, 7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4, 5, 5, 6, 7</td>
</tr>
<tr>
<td>IV 9a-fluoro, 16a-hydroxyprednisolone</td>
<td>5</td>
<td>6, 7, 8, 8, 9</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>7, 8, 8, 9, 9</td>
</tr>
<tr>
<td>V 9a-fluoro, 16a-hydroxyprednisolone, 16a, 17a-acetonide</td>
<td>5</td>
<td>5, 6, 6, 7, 7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5, 5, 6, 7, 7</td>
</tr>
<tr>
<td>VI 9a-fluoro, 16a-hydroxyprednisolone, 16a, 17a-acetonide, 21 hemisuccinate</td>
<td>5</td>
<td>S, S, S, S, S</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>S, S, S, S, S</td>
</tr>
<tr>
<td>VII 9a-fluoro, 16a-hydroxyprednisolone, 16a, 17a-acetonide, 21 sodium diphasate</td>
<td>5</td>
<td>8, 8, 9, 9, 10</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>7, 7, 8, 8, 9</td>
</tr>
<tr>
<td>VIII 9a-fluoro, 16a-hydroxyprednisolone, 16, 21 dihemisuccinate</td>
<td>5</td>
<td>S, S, S, S, S</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>S, S, S, S, S</td>
</tr>
</tbody>
</table>

* See Table I for explanation of S.
CORTICOSTEROIDS AND HOST RESISTANCE

On the one hand, injection of steroids I, III, IV, V, and VII shortened the survival of animals infected with *C. kutscheri, S. aureus, and K. pneumoniae*; on the other hand, steroids II, VI, VIII had no effect upon host resistance of mice to these infections. Even more striking was the difference between the two groups of steroids in mice infected with *L. monocytogenes*. In this case, compounds I, III, IV, V, and VII caused death of all animals, whereas compounds II, VI, and VIII allowed survival.

**TABLE III**  
Effect of Steroids upon Experimental Infection of NCS mice with *C. kutscheri, K. pneumoniae, S. aureus, and L. monocytogenes*

<table>
<thead>
<tr>
<th>Steroids tested</th>
<th>Average day of death after infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>C. kutscheri</em></td>
</tr>
<tr>
<td>Control (0.2 ml saline)</td>
<td>9.6</td>
</tr>
<tr>
<td>I Hydrocortisone acetate</td>
<td>3.4</td>
</tr>
<tr>
<td>II 6α-methylprednisolone, 21 sodium hemisuccinate</td>
<td>9.5</td>
</tr>
<tr>
<td>III 9α-fluoro, 16α-methylprednisolone acetate</td>
<td>2.6</td>
</tr>
<tr>
<td>IV 9α-fluoro, 16α-hydroxyprednisolone</td>
<td>2.4</td>
</tr>
<tr>
<td>V 9α-fluoro, 16α-hydroxyprednisolone, 16α, 17α-acetonide</td>
<td>2.6</td>
</tr>
<tr>
<td>VI 9α-fluoro, 16α-hydroxyprednisolone, 16α, 17α-acetonide, 21 hemisuccinate</td>
<td>9.8</td>
</tr>
<tr>
<td>VII 9α-fluoro, 16α-hydroxyprednisolone, 16α, 17α-acetonide, 21 disodium phosphate</td>
<td>3.6</td>
</tr>
<tr>
<td>VIII 9α-fluoro, 16α-hydroxyprednisolone, 16, 21 dihemisuccinate</td>
<td>9.8</td>
</tr>
</tbody>
</table>

S, survived, but autopsied 15 days after infection. No gross pathology could be distinguished.

**Comparative Effect of Steroids upon Peritoneal Exudate Cells.**—

Eight groups of five mice of both sexes were injected with steroids (10 mg per mouse), and control groups were given 0.2 ml of saline. 24 hr later they were injected intraperitoneally with 1 ml of tryptose broth. 4 hr after this last injection the mice were killed by cervical dislocation, and peritoneal cells were withdrawn. Following incubation of these cells, the total number of cells, the number of inactive macrophages, and the number of spreading macrophages were recorded.

As can be seen in Fig. 3 a, polymorphonuclear leukocytes, lymphocytes, and macrophages are present in the peritoneal exudate. Among these cells, macrophages in the resting state are easy to recognize from other cells with their
Figs. 3 a–3 d. Effect of hydrocortisone acetate upon peritoneal cells of the mouse. M, macrophages; P, polymorphonuclear leukocytes; L, lymphocytes; and E, erythrocytes.

Fig. 3 a, peritoneal washing of a normal mouse as observed before incubation; Fig. 3 b, peritoneal washing of a normal mouse after 30 min incubation at 37°C showing spreading of macrophages and polymorphonuclear leukocytes; Fig. 3 c, peritoneal washing of hydrocortisone acetate–treated mouse before incubation; and Fig. 3 d, peritoneal washing of hydrocortisone acetate–treated mouse after 30 min incubation at 37°C showing no cellular spreading.
brownish center as seen with the phase microscope. 30 min later, polymorphonuclear leukocytes and macrophages have spread out on the bottom of the counting chamber (Fig. 3 b). In contrast, in peritoneal exudates from mice injected with steroids I, III, IV, V, VII, we noticed not only a decrease in the total number of peritoneal cells (Fig. 3 c), but also a striking decrease of the number of macrophages which had spread on the glass after 30 min of incubation (Fig. 3 d). In Table IV are summarized the results of five experiments, evaluated in this way.

TABLE IV
Effects of Steroids upon the Total Number of Peritoneal Cells, upon the Number of Macrophages and Their Spreading Ability

<table>
<thead>
<tr>
<th>Steroids tested</th>
<th>Total No.* of peritoneal cells</th>
<th>No.* of macrophages</th>
<th>No.* of spreading macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Hydrocortisone acetate</td>
<td>55</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>II 6α-methylprednisolone, 21 sodium hemisuccinate</td>
<td>60</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>III 9α-fluoro, 16α-methylprednisolone acetate</td>
<td>37</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>IV 9α-fluoro, 16α-hydroxyprogesterone</td>
<td>39</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>V 9α-fluoro, 16α-hydroxyprogesterone, 16α, 17α-acetonide</td>
<td>37</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>VI 9α-fluoro, 16α-hydroxyprogesterone, 16α, 17α-acetonide, 21 hemisuccinate</td>
<td>75</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>VII 9α-fluoro, 16α-hydroxyprogesterone, 16α, 17α-acetonide, 21 disodium phosphate</td>
<td>50</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>VIII 9α-fluoro, 16α-hydroxyprogesterone, 16α, 21-hemisuccinate</td>
<td>70</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Control (0.2 saline s.c.)</td>
<td>129</td>
<td>69</td>
<td>50</td>
</tr>
</tbody>
</table>

* Multiply (X 10^6) to obtain No. cells/ml of peritoneal exudate.

There was a decrease in the total number of peritoneal cells obtained from steroid-treated mice compared with control animals. A marked difference, however, was observed in the effects of compounds I, III, IV, V, and VII compared with compounds II, VI, and VIII upon the spreading property of macrophages upon glass surfaces. The first-mentioned group decreased or even inhibited spreading, but compounds II, VI, and VIII displayed no appreciable effect. Thus, as in the previous experiments, these steroids can be classified into two distinct groups.

DISCUSSION

Since the discovery of the antiinflammatory property of adrenal steroids, a great number of investigations have been undertaken in order to elucidate the mechanism of their action and also to synthesize new compounds devoid of
toxic effects and, if possible, exhibiting higher antiinflammatory activity (11–13). Other investigators have focused their attention on the decrease of host resistance to infection in corticoid-treated animals (1–7, 16–18).

Among the steroids which we tested in this study, only four of them had been tested for their antiinflammatory, thymolytic, and glucocorticoid activities in a comparative study (12); namely, compounds I, III, IV, and V. Since we were not aware of any comparative investigation concerning the antiinflammatory activities of compounds II, VI, VII, and VIII, it seemed useful to test these compounds in comparison with compounds I, III, IV, and V for antiinflammatory properties and the action on host resistance to infection.

The findings reported in this paper and their possible implications can be considered under the following headings.

Antiinflammatory Activity of the Steroids Used in this Study.—The high doses used in these experiments and the imprecision of the technic did not allow us to evaluate closely the differences in activity of the drugs tested. Nevertheless, with this simple technic it was possible to obtain information quickly concerning the antiinflammatory activity of the steroids. Study of corticoid antiinflammatory property was not the chief purpose of this work and we asked only for clear-cut information concerning this activity. It was possible to detect the early phase activity of the compounds and the relatively low activity of hydrocortisone acetate in comparison with the other drugs. This last observation is in agreement with results obtained by other investigators (12). Furthermore, the antiinflammatory test allowed us to distinguish the earlier action of compounds II and VII. The high water solubility of these two compounds may allow a higher rate of diffusion in the tissue of mice and therefore an earlier appearance of activity.

Comparative Activities of Different Steroids on Host Resistance to Infection.—The effects of these corticoids, both from the point of view of latent and experimental infections, lead us to consider two groups of compounds. In the first group are those corticoids which are able, when injected in latently or experimentally infected animals respectively, to activate latent corynebacterial infection and to decrease the survival time of infected animals. These compounds are I, III, IV, V, and VII. In the second group are corticoids which were not able, in our experimental conditions, either to activate latent corynebacterial infection or to decrease the survival time of infected animals. These compounds are II, VI, and VIII. In other words, this group of steroids, despite their antiinflammatory activity, did not decrease the host resistance to infection. Such differences in corticosteroids in regard to their effect on host resistance to bacterial infection has never been previously reported. Frenkel (14), studying the effects of "modified corticoids" on hamsters infected with Besnoitia jellysoni and Toxoplasma gondii, found that cortisone was the least active com-
pound and that compounds I, IV, V, III were, in this order, of increasing ac-
tivity.

Relationship between Chemical Structure of the Steroids Used and Their Ac-
tivity on Host Resistance to Infection.—Among the corticoids devoid of activity
on host resistance to infection one can notice the presence of a double bond
between position 1 and 4, methyl group at 6α, fluoro at 9α and acetonide at
16α,17α; all of these chemical modifications are known to increase the anti-
flammatory property of the corticosteroid molecule (15). It should also be
noted that these three compounds (II, VI, VIII) lack the hydroxyl group in
position 21. But such modifications are present also on other compounds which
decrease host resistance to infection and have a lower antiinflammatory ac-
tivity than drugs II, VI, and VIII. These three steroids are characterized by the
addition to the molecule of hemisuccinic acid groups and the purpose of inves-
tigations now under way is to elucidate the importance of succinic acid on the
biologic effect of corticosteroids.

Relationship of Solubility and Activity of Steroids on Host Resistance to In-
flection.—The physical characteristic of solubility cannot explain the differ-
ces observed among the steroids used. Indeed, compound II which is without action
on host resistance to infection, is as soluble as compound VII, a corticosteroid
which decreases host resistance to infection. Furthermore, it was shown that
compound III, which is one of the more potent antiinflammatory and infection-
provoking corticosteroids, is more soluble than hydrocortisone which is less
potent (14). Therefore, we do not think that different solubilities can explain
the differences observed in this study.

Reflections Upon Corticosteroid Activity on Host Resistance to Infection at
the Cellular Level.—The decrease of the total number of peritoneal cells in
corticosteroid-treated mice which occurs with all drugs tested is, we believe,
another illustration of the inhibition of diapedesis by corticosteroids (4–7).
Since it has been reported by many investigators that phagocytic cells from
cortisone-treated animals do not show any alteration in their ingestion and
digestion capacities (16–18), our observation that certain compounds adminis-
tered in vivo inhibited the spreading property of macrophages on glass surfaces
seems of interest. Indeed, such compounds were the ones which decreased the
host resistance of animals to infection. In striking contrast, steroids containing
succinate groups did not inhibit macrophage spreading and did not alter the
response of mice to infection. Are these observations of prime importance in
elucidating mechanisms whereby infection-provoking corticosteroids decrease
host resistance to infection?

"Paralysis" of macrophages has been reported to occur in the spleen of
cortisol-treated mice (19). It is possible, therefore, that such inhibition of
macrophage mobilization explains, in part, the lack of host defense against
bacteria solely because the macrophages cannot migrate into the infected
tissue area. How can the influence of succinate groups upon corticosteroid ac-
tion as observed at the macrophage level be correlated with steroid effects upon other functions? Does the succinate group interfere with the energy-liberating mechanism of the cell, namely, the function of glycolysis? From knowledge of the importance of succinate in the tricarboxylic acid cycle, succinate could possibly decrease the known disturbing effect of corticosteroids on glycolysis (20). Whatever the reasons may be for such differences between succinate-containing corticoids and other steroids tested, one can conclude that the infection-provoking properties of the corticoids are not correlated with their antiinflammatory effects.

SUMMARY

In a comparative study concerning the effect of corticosteroids on host resistance to infections, five compounds were found to decrease host resistance, while three did not have this property, although all eight compounds were highly antiinflammatory.

The compounds capable of decreasing host resistance were (I) hydrocortisone acetate; (III) 9α-fluoro,16α-methylprednisolone acetate; (IV) 9α-fluoro,16α-hydroxyproglinsolone; (V) 9α-fluoro,16α-hydroxyproglinsolone,16α-17α-acetonide; and (VII) 9α-fluoro,16α-hydroxyproglinsolone,16α,17α-acetonide,21 disodium phosphate. Following a single injection of 10 mg of any of these compounds, latent corynebacterial infection was provoked into active pseudotuberculosis. Also, mice injected with these corticosteroids were more susceptible to infection with Corynebacterium kutscheri, Staphylococcus aureus, Klebsiella pneumoniae, or Listeria monocytogenes. These same corticosteroids inhibited the ability of mouse peritoneal macrophages to spread on glass surfaces.

The three compounds incapable of decreasing host resistance, although highly antiinflammatory, were: (II) 6α-methylprednisolone, 21 sodium hemisuccinate; (VI) 9α-fluoro,16α-hydroxyproglinsolone,16α,17α-acetonide, 21 hemisuccinate; and (VIII) 9α-fluoro,16α-hydroxyproglinsolone,16, 21 dihemisuccinate. These three compounds were also unable to inhibit the spreading of macrophages on glass.

The importance of succinate group bound to the corticosteroid molecule as hemisuccinate is emphasized since it is seen that the infection-provoking property can be dissociated from the antiinflammatory property. This finding may be of practical consequence in selecting a corticosteroid for treatment in disease, and also shows that one cannot use, indifferently, corticosteroids only on the basis of their common antiinflammatory property.

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