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Effects of Indomethacin on Acute, Subacute, and Latent Infections in Mice and Rats

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The comparative effect of indomethacin and hydrocortisone on the resistance of mice or rats to various acute, subacute, and latent bacterial infections was investigated. Large daily doses of indomethacin and hydrocortisone administered to mice challenged with bacterial pathogens, including *Klebsiella pneumoniae* AD, *Salmonella schottmuelleri* 3010, *Staphylococcus aureus* (Smith), *Streptococcus pyogenes* C203, *Salmonella pullorum* #2, *Proteus vulgaris* 1810, and *Pseudomonas aeruginosa* 2616, revealed that in essentially all of these acute infections, the mortality of the infected mice treated with indomethacin was essentially identical to that found in the infected controls. In contrast, hydrocortisone often lowered the resistance of mice to these acute infections. In a more chronic bacterial infection due to *Corynebacterium kutscheri*, hydrocortisone produced striking deleterious effects on resistance, whereas indomethacin administration in doses approaching the maximal tolerated level caused no observable adverse effects on host resistance. Indomethacin fed continuously to rats for 80 days, at maximal tolerated levels, caused no observable adverse effects on the host-parasite relationship of rats which were shown to harbor various latent infections. Hydrocortisone administration, however, lowered the resistance of rats as evidenced by increased mortality related directly to extensive bacterial infection. Insofar as infection is concerned, indomethacin behaved like other nonsteroid anti-inflammatory agents such as aspirin and phenylbutazone.

Presently, there are a number of therapeutic agents available for the symptomatic treatment of rheumatoid arthritis and allied disorders. Among the drugs most widely used are the salicylates, the adrenal cortical steroids, indomethacin, and phenylbutazone. The basic mechanisms by which these drugs exert their beneficial actions in connective tissue disease remains unsolved, but all appear to affect inflammation and/or immunological processes in mesenchymal and connective tissue (2, 5, 12). In addition, these agents relieve certain types of pain and reduce fever.

Inflammation and fever are often the principal clinical signs of infection. Moreover, the inflammatory reaction and prompt activation of immunological processes following microbial invasion are generally recognized as important defense mechanisms against infection. Therefore, drugs which suppress inflammation or immunological processes, or both, or agents known to possess analgesic and antipyretic action, must be viewed carefully with respect to their possible deleterious effect on an infectious process per se and with regard to their action in masking the early signs of infection.

Within recent years, a new, highly potent anti-inflammatory agent named indomethacin was introduced into clinical medicine. The drug has been widely used in the treatment of rheumatoid arthritis (4), osteoarthritis (20), and gout (17). Indomethacin's unique chemical structure, 1-(*p*-chlorobenzolyl) - 5 - methoxy - 2 - methylindole - 3-acetic acid, differentiates it from the salicylates, corticosteroids, phenylbutazone-like compounds, and colchicine. The drug exerts strong analgesic and antipyretic action, and like aspirin and other nonsteroid anti-inflammatory agents, indomethacin might be expected to reduce fever and pain associated with various pathological states, including certain infections.

The present paper is concerned primarily with investigations dealing with the effect of indomethacin on acute, subacute, and latent bacterial infections in mice or rats. Since corticosteroids were known to reduce the resistance of animals to many experimental infections, hydrocortisone

was used as a positive control in almost all of the experiments.

MATERIALS AND METHODS

Animals. Female pathogen-free mice (CD-1, 18 to 22 g) of the HaM/ICR Swiss strain (Charles River Mouse Farms, Inc., North Wilmington, Mass.) and female CF#1 mice (Carworth Farms, Inc., New City, N.Y.) were employed. The study extended over several years and approximately 3,200 mice were used. In the majority of the mouse experiments, groups of 10 animals, totaling approximately 150 per test, were used and each experiment was repeated a number of times at different periods of the year. Male Sprague-Dawley rats, weighing 130 to 150 g, were obtained from the Holtzman Co., Madison, Wis. All animals were housed in air-conditioned quarters and maintained on Purina Laboratory Chow (Ralston Purina Co., St. Louis, Mo.) and water ad libitum. Approximately 920 rats were used in these studies.

Drugs. Hydrocortisone (Merck), as the free alcohol, and indomethacin were used throughout these investigations. The drugs were ground to a fine powder and suspended in Merck Aqueous Vehicle No. 1 (sodium carboxymethylcellulose, 0.5%; polysorbate 80, 0.4%; benzyl alcohol, 0.9%; sodium chloride, 0.9%; and water for injection, qs) or were incorporated in the diet. Details of the dose levels, treatment schedule, and route of drug administration are given in the tables. In the majority of the experiments, indomethacin was given in a range of dose levels which, at times, approached toxic levels. The hydrocortisone levels were selected on the basis of previous experience and on published results of other investigators (1, 3, 18).

Bacterial cultures and methods used to induce infection. The following cultures were employed: *Klebsiella pneumoniae* AD, *Salmonella schottmuelleri* 3010, *Staphylococcus aureus* (Smith), *Streptococcus pyogenes* C203, *Salmonella pullorum* #2, *Proteus vulgaris* 1810, *Pseudomonas aeruginosa* 2616, and *Corynebacterium kutscheri.* Each of the above strains was maintained in the lyophilized state. For each experiment, a new ampoule of the bacterial strain was reconstituted and grown in broth.

Latent infections. Experiments were undertaken in rats to determine whether indomethacin would disturb host-parasite equilibrium and activate quiescent infections in animals which were known to harbor latent infections. Previous experimentation had shown that several strains of rats often harbored latent infections which could be readily activated by the administration of adrenal cortical steroids. In the present study, 240 male Sprague-Dawley rats were subdivided by random distribution into eight groups of 30 rats each and fed diets containing either indomethacin or hydrocortisone, or no drug. Treatment extended over an 80-day period; drug intake was determined by weekly food consumption measurements and recordings of the body weight. In view of the eating habits of rats, the animals ingested the drugs day and night throughout the 80-day treatment period. Dose levels of indomethacin and hydrocortisone administered are shown in Fig. 1. The highest indomethacin level approached the maximal tolerated dose. Amounts of drug administered were large in terms of anti-inflammatory activity and in terms of the recommended dose for man. Mortality was recorded daily and, unless the animal was cannibalized, all rats were autopsied and examined for signs of infection. In almost all animals which died, the heart blood was cultured, and the general nature of the microorganisms causing infection was established. No attempt was made to search for microorganisms other than bacteria. Upon terminating the experiment, all surviving animals were sacrificed. The kidneys, spleen, liver, and heart blood were removed aseptically, homogenized, and cultured in nutrient agar, and the number and nature of the microorganisms cultured from each organ were recorded. The major organs were also examined grossly for evidence of infection.

All data presented in this paper were analyzed statistically and conclusions were based on P values ranging between <0.01 to <0.05.

RESULTS

Acute bacterial infection in mice. At times, the results of individual experiments were highly variable, therefore large numbers of mice had to be used and experiments were repeated many times. The results obtained with *S. pyogenes* C203 and details of the experimental design used in most of the acute infections are shown in Table 1. The findings of representative experiments with each of six other acute bacterial infections in mice are summarized in Tables 2 and 3. Generally, hydrocortisone decreased resistance to these infections, whereas, with the few exceptions cited below, indomethacin caused no observable adverse effects. In some instances, the survival rate appeared to be somewhat greater in mice treated with indomethacin. The tendency for hydrocortisone to lower resistance to infection was particularly evident in mice infected with *S. pyogenes* and *S. pullorum* at the 10^{-8} and 10^{-6} culture dilution, respectively, *K. pneumoniae* at 10^{-6} and 10^{-7} levels of infection, *S. aureus* at 2×10^{-4} culture dilution, *P. aeruginosa* at the 10^{-5} level of infection, and *S. schottmuelleri* at 2×10^{-3} and 2×10^{-4}. Hydrocortisone did not lower the resistance of mice to *P. vulgaris*; the steroid appeared to increase the survival rate at the 10^{-5} and 10^{-6} level of this infection. In general, the deleterious action of hydrocortisone observed in most infections appeared to increase as the dose levels of the steroid were increased. In agreement with the published literature, the adverse effects were particularly evident when massive doses of the steroid were given (as illustrated in our studies with *C. kutscheri*, below).

TABLE 1. *Comparative effect of indomethacin and hydrocortisone on resistance of mice to infection*[a]

Treatment	Dose (μg per mouse per day)	Culture dilution	No. of mice	Days after infection (no. living)										Surviving (%)
				1	2	3	4	5	6	7	8	9	10	
Indomethacin	100	2×10^{-6}	19	16	7	4	3	3	3	3	3	3	3	16
	50	2×10^{-6}	20	17	7	5	3	3	3	3	3	3	3	15
	25	2×10^{-6}	20	14	5	1	1	1	1	1	1	1	1	5
Hydrocortisone	500	2×10^{-6}	10	0	0	0	0	0	0	0	0	0	0	0
	250	2×10^{-6}	10	3	1	0	0	0	0	0	0	0	0	0
Controls		2×10^{-6}	20	17	5	2	1	1	1	1	1	1	1	5
Indomethacin	100	2×10^{-7}	20	20	9	3	2	2	2	2	2	2	2	10
	50	2×10^{-7}	20	19	11	6	5	5	5	5	5	5	5	25
	25	2×10^{-7}	20	19	11	6	2	2	2	2	2	2	2	10
Hydrocortisone	500	2×10^{-7}	10	1	0	0	0	0	0	0	0	0	0	0
	250	2×10^{-7}	10	6	2	0	0	0	0	0	0	0	0	0
Controls		2×10^{-7}	20	20	9	3	2	2	2	2	2	2	2	10
Indomethacin	100	2×10^{-8}	20	20	17	10	9	9	9	9	9	9	9	45
	50	2×10^{-8}	20	20	14	10	9	9	9	9	9	9	9	45
	25	2×10^{-8}	20	20	16	12	11	11	11	11	11	11	11	55
Hydrocortisone	500	2×10^{-8}	10	6	3	2	2	2	2	0	0	0	0	0
	250	2×10^{-8}	10	9	3	2	1	1	1	1	0	0	0	0
Controls		2×10^{-8}	20	20	14	11	9	9	9	9	9	9	9	45

[a] Infection: *Streptococcus pyogenes* C203; Brain Heart Infusion, 0.5 ml, intraperitoneally. Treatment: indomethacin orally, hydrocortisone subcutaneously; drugs administered daily in two divided doses for 5 days, beginning 2 days prior to challenge and continued as a single dose for 5 additional days.

The lack of deleterious effects of indomethacin on these acute infections, or at times, the tendency of the drug to increase the survival rate of infected mice, may be noted most readily in infections due to *S. aureus*, *S. pyogenes*, *P. vulgaris*, and *S. pullorum* (Tables 1, 2, and 3). If latent infections were present in any of these animals, apparently indomethacin did not activate the infections, judging from mortality figures and heart-blood culture studies. In *K. pnuemoniae* infections, indomethacin at the 50 and 100 μg/mouse levels appeared to enhance the survival rate, whereas, the 25 μg/mouse level appeared to have an adverse effect. However, these values were not statistically significant. The only unusual finding in the mice treated with indomethacin occurred in animals infected with the 2×10^{-3} culture dilution of *S. schottmuelleri* and treated with the highest level of indomethacin (Table 2). The increased mortality would appear to be due to drug toxicity, although the toxic effects of large numbers of gram-negative bacteria and their endotoxins may have contributed to the findings.

Subacute infections in mice. With few exceptions, the findings with *C. kutscheri* were far more uniform and reproducible than were those obtained with the more acute bacterial infections. However, experimentation during the summer months was avoided to reduce complicating factors of latent infections which appear to be more prevalent at this time. In addition, the duration of the infection was such that it offered ample time for the drugs to exert an action, if any, on the various defense mechanisms called into action by the host. The uniform response of mice to this infection may be noted from the similarity in the survival time and rate of several groups of control mice infected and maintained without treatment under identical conditions (Table 4).

Confirming previous reports (1, 3, 8, 18), hydrocortisone, at all levels of treatment, lowered the resistance of mice to this infection. The most striking findings occurred at the 10^{-1} level of infection and at the highest level of steroid treatment. However, even the lowest dose level of hydrocortisone reduced the resistance of mice to this infection (Table 4). Indomethacin, even at levels which approached the maximal tolerated dose, caused no observable adverse effects on host resistance. The survival time and rate were essentially identical in the untreated, infected control animals and in the mice treated with indomethacin. Moreover, autopsy findings and blood-culture studies indicated that the disease

progressed approximately at the same rate and degree in both the control mice and the animals treated with indomethacin.

K. pneumoniae infections in rats. In view of the negative findings in most experiments with this animal species, the results of only certain experiments are presented in tables and figures. In all experiments dealing with this infection, indomethacin caused no observable adverse effects on the resistance of rats to *K. pneumoniae*, even when the drug was given in amounts which approached the maximal tolerated level. Similarly, hydrocortisone usually caused no significant deleterious effects on host resistance to infection, except at the highest dose level of 20.6 mg per kg per day fed in the diet over a 24-day period (Table 5). Perhaps the most interesting finding was noted in rats treated with large single doses of

TABLE 2. *Comparative effect of indomethacin and hydrocortisone on resistance of mice to infection*[a]

Infection	Culture dilution	Indomethacin (μg per mouse per day)			Hydrocortisone (μg per mouse per day)		Control
		100	50	25	500	250	
S. aureus (Smith)[b]	2×10^{-2}	10[c]	0	0	0	0	0
	2×10^{-3}	85	65	45	10	60	35
	2×10^{-4}	100	100	100	60	90	100
P. vulgaris 1810[d]	10^{-4}	45	40	30	10	10	10
	10^{-5}	60	65	45	50	20	25
	10^{-6}	89	90	80	80	70	50
S. schottmuelleri 3010[b]	2×10^{-2}	5	5	0	0	0	5
	2×10^{-3}	10	50	50	0	0	70
	2×10^{-4}	85	95	95	20	100	95

[a] Treatment: indomethacin given orally, hydrocortisone subcutaneously; drugs administered daily in two divided doses for 5 days, starting 2 days prior to challenge, and as a single daily dose for 5 additional days. Each group represents 20 animals.
[b] Broth dilution (Brain Heart Infusion), 0.5 ml intraperitoneally.
[c] Percentage of mice surviving on day 10.
[d] In 5% hog gastric mucin, 0.5 ml intraperitoneally.

TABLE 3. *Comparative effect of indomethacin and hydrocortisone on resistance of mice to infection*[a]

Infection	Culture dilution	Indomethacin (μg per mouse per day)			Hydrocortisone (μg per mouse per day)		Control
		100	50	25	500	250	
K. pneumoniae AD[b]	10^{-5}	58[c]	35	16	0	0	30
	10^{-6}	84	70	55	0	10	70
	10^{-7}	85	75	55	0	0	75
P. aeruginosa 2616[d]	10^{-4}	32	35	25	20	30	30
	10^{-5}	47	65	60	10	60	75
	10^{-6}	80	90	95	60	70	65
S. pullorum #2[d]	2×10^{-4}	30	20	10	10	0	15
	2×10^{-5}	40	25	40	0	10	5
	2×10^{-6}	53	75	45	0	30	40

[a] Treatment: indomethacin given orally, hydrocortisone subcutaneously; drugs administered daily in two divided doses for 5 days, starting 2 days prior to challenge and as a single daily dose for 5 additional days. Each group represents 20 animals.
[b] Broth dilution (Brain Heart Infusion); 0.5 ml intraperitoneally.
[c] Percentage of mice surviving on day 10.
[d] In 5% hog gastric mucin; 0.5 ml intraperitoneally.

TABLE 4. *Effect of indomethacin and hydrocortisone on subacute infection in mice*[a]

Treatment[b]	Daily dose (μg/mouse)	Culture dilution	Time (days)							
			6	8	10	12	14	16	18	20
Indomethacin	100	10^{-1}	10[c]	10	9	9	9	8	8	8
	50	10^{-1}	10	10	9	9	9	9	9	9
	25	10^{-1}	10	10	10	8	8	8	7	7
	12.5	10^{-1}	10	10	8	8	8	7	7	7
	6.25	10^{-1}	10	10	9	9	9	9	9	9
Hydrocortisone	2,000	10^{-1}	9	6	3	0				
	1,000	10^{-1}	10	6	4	2	2	1	1	1
	500	10^{-1}	9	7	4	2	1	1	1	1
	250	10^{-1}	10	8	8	7	5	4	4	4
	125	10^{-1}	10	9	8	5	5	4	3	3
Control	AV[d]	10^{-1}	8	7	7	7	7	6	5	5
	AV[d]	10^{-1}	10	10	8	7	7	7	7	7
	AV[d]	10^{-1}	10	10	9	9	8	8	8	8
	AV[d]	10^{-1}	10	10	10	9	9	9	9	9
	AV[d]	10^{-1}	10	10	8	7	7	7	7	7
Indomethacin	100	10^{-2}	10	10	10	10	10	10	10	10
	50	10^{-2}	10	10	10	10	10	10	10	10
	25	10^{-2}	10	10	10	10	10	10	10	10
Hydrocortisone	1,000	10^{-2}	10	9	8	7	6	5	5	5
	500	10^{-2}	10	10	9	7	6	5	4	4
	250	10^{-2}	10	10	10	10	9	7	6	6
Controls	AV	10^{-2}	10	10	10	10	10	10	10	10
	AV	10^{-2}	10	10	10	10	10	10	10	10
	AV	10^{-2}	10	10	10	10	10	10	10	10

[a] Infection: *Corynebacterium kutscheri*, 0.05 ml intranasally.
[b] Treatment: daily dose divided into two equal portions, administered orally at 9 AM and 4 PM. Treatment started 2 days prior to challenge and continued for the duration of the experiment.
[c] Number of mice surviving of 10 mice tested in each group.
[d] Merck Aqueous Vehicle No. 1.

indomethacin and challenged 48 hr later with a lethal dose of *K. pneumoniae*. Indomethacin, at the 10 mg/kg level, significantly increased the resistance of rats to this infection and, in contrast to the untreated control rats, most animals survived the infection when treated previously with indomethacin (Table 6). Other studies (*in preparation*) show that this effect persisted for many weeks and was due to changes in the wall of the gastrointestinal tract, which allowed gram-negative bacteria and endotoxins to enter the peritoneal cavity and general circulation. The striking beneficial effects of endotoxins on host resistance to infection have been reported (10, 14, 16).

Latent infections. Mortality over the 80-day period in the two groups of control rats was 10 and 17%, respectively. Cultures of the various organs of control animals, sacrificed when the experiment was terminated, indicated that small numbers of microorganisms were present in the spleen, liver, or kidneys, or in all of these organs, of most of the animals. Several types of microorganisms were found, including streptococci, staphylococci, gram-negative rods, and *C. kutscheri*. The latter microorganism is a common pathogen found in rats and mice, and many investigators have shown that the corticosteroids lower the resistance of mice and rats to this latent infection (1, 15). A small percentage of the rats had healed lesions in the lungs and kidneys, which were suggestive of a previous active infection. The mortality of the animals treated with hydrocortisone at levels of 4.5, 10, and 21.4 mg per kg per day over the 80-day period was 30, 50, and 79%, respectively (Fig. 1). All deaths were related to extensive bacterial infection, as determined by blood-culture studies and the gross

TABLE 5. *Influence of hydrocortisone and indomethacin on resistance of rats to infection with Klebsiella pneumoniae* AD[a]

Treatment[b] (avg daily dose)	No. dead[c]	No. dead of toxicity and/or latent infection	Per cent dead
Hydrocortisone			
5.0 mg per kg per day	1	0	5
9.95 mg per kg per day	3	0	15
20.6 mg per kg per day	8	0	40
Indomethacin			
0.99 mg per kg per day	1	0	5
2.1 mg per kg per day	0	0	0
4.6 mg per kg per day	2	1 (toxicity)	10 (toxicity)
Controls	1	0	5
Controls	0	0	0

[a] Infection: *Klebsiella pneumoniae* AD; 0.5 ml of a 10^{-4} dilution in 4% hog gastric mucin by the intraperitoneal route.

[b] Treatment: drugs in ground Purina chow; dosing started 4 days preinfection and continued for 20 days postinfection.

[c] Of 20 animals in each group.

TABLE 6. *Increased survival of infected[a] rats treated with indomethacin*

Treatment[b]	Dose (mg/kg)	No. of rats	Time (days)				
			2	4	6	8	10
Indomethacin	0.25	15	93[c]	40	33	27	27
	1.0	15	100	67	33	33	33
	4.0	15	93	73	47	40	40
	10.0	10	100	100	100	100	100
Controls		28	100	46	29	21	21

[a] Infection: *Klebsiella pneumoniae* AD (0.5 ml, 5×10^{-4}) intraperitoneally in 5% hog gastric mucin.

[b] Treatment: single oral dose 48 hr before challenge.

[c] Percentage of rats surviving.

findings at autopsy. The incidence and degree of infection detected in the various organs of surviving animals treated with hydrocortisone were much greater than those found in the controls. Usually, deaths occurred earlier at the higher levels of steroid treatment. The mortality of the animals treated with indomethacin at levels of 0.4, 0.9, and 2.1 mg per kg per day was 3, 3, and 17%, respectively. The nature of the infections and the incidence of infection were essentially the same as in the control animals. The gross signs of infection found in the surviving animals treated with indomethacin, sacrificed after 80 days of treatment, were essentially identical in number and character to those noted in the control rats. Moreover, the numbers and nature of the microorganisms isolated from the spleen, liver, and kidneys paralleled those found in the control animals. Finally, some of the late deaths in these experiments may have been due to cross or acquired infection, rather than the activation of latent infection per se. However, there was no way to determine the origin of an infection in any given animal. In either case, indomethacin caused no detectable adverse effect, whereas hydrocortisone lowered the resistance of rats to those infections, whatever the origin of the latter may have been late in the treatment period.

DISCUSSION

The data presented herein indicate that, by and large, repeated administration of indomethacin in a range of dose levels, which at times bordered on toxic or lethal levels, caused no observable deleterious effects on the survival of mice or rats infected with various bacterial pathogens. In the majority of the experiments, the mortality of the infected mice and rats treated with indomethacin was essentially identical to that found in the infected controls which had not been treated with the drug. Similarly, indomethacin fed continuously for 80 days, at maximal tolerated levels, appeared to induce no adverse effects on the host-parasite relationship of rats which were shown to harbor various latent infections. The overall findings suggest that indomethacin behaves like aspirin and other nonsteroid anti-inflammatory agents, insofar as infection is concerned. The results of these investigations are in agreement with the findings in experimental tuberculosis (13).

In contrast to the findings with indomethacin

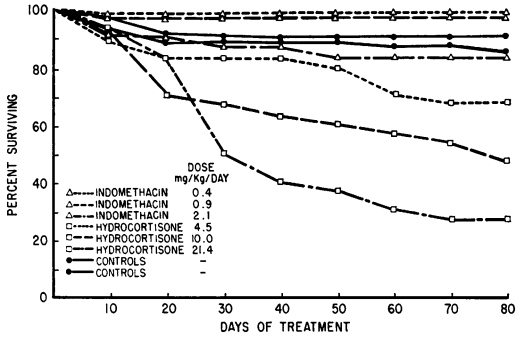

FIG. 1. *Effect of indomethacin and hydrocortisone on latent infections in rats. Drugs administered in the diet for 80 days.*

and as reported by numerous investigators (1, 3, 8, 11), hydrocortisone often lowered the resistance of mice and, at times, of rats to both induced and latent infections. In many instances, the adverse effects were quite marked. However, this steroid lowered resistance to infectious agents only when large, pharmacological doses were administered. At such levels, the corticosteroids are known to produce numerous and diversified actions, including effects on carbohydrate, protein, fat, and purine metabolism. Furthermore, it is common knowledge that at these high dose levels, these steroids cause marked weight loss and a negative nitrogen balance, and influence the functional capacity of numerous organs and tissues of the body. The latter actions include marked atrophy of the lymphoid tissue (6, 9) and suppression of the functions of the reticuloendothelial system (19). Both effects are obviously important in immunological processes and in the disposal of pathogenic microorganisms.

Because of the marked difference in the pharmacological properties of indomethacin and hydrocortisone, some caution must be exercised in attempting to compare the relative effects of the two drugs on host resistance to experimental infection. Indeed, it would appear more reliable to evaluate each drug individually by comparing the survival rate of the drug-treated and non-drug-treated infected animals. Thus, aside from the fact that each drug may be absorbed, metabolized, and excreted at different rates in various animal species, their comparative toxicity was such that, by and large, it was not possible to administer equal and meaningful amounts of the two drugs on a weight basis. With few exceptions, the dose levels of hydrocortisone required to lower resistance to infection were so large that comparable doses of indomethacin were toxic or lethal. Conversely, in general, hydrocortisone caused no adverse effects when the dose levels were reduced to the maximal tolerated levels of indomethacin. However, according to the results of the granuloma inhibition assay in rats, indomethacin was reported to be approximately four times as active as hydrocortisone (21, 22). Assuming that these findings apply to mice as well as to rats, the two drugs were administered at equivalent anti-inflammatory dose levels in many of the experiments reported in the present investigations. In the studies with *C. kutscheri* and those concerned with activation of latent infection in rats, the drugs were also given in a few instances, at levels which were approximately equivalent even on a weight basis.

The contrasting findings between the steroid and nonsteroid agents, and the observation that the latter do not appear to lower resistance to infection, raise a number of interesting points for consideration. Data to explain fully the reasons for the differences in the behavior of the two classes of drugs in infectious disease are not available to date. Recently, Fauve and Pierce-Chase, working with a number of anti-inflammatory steroids, concluded that anti-inflammatory action per se does not account for the detrimental action of these agents in infections (7). From the present investigations, quantitative data are not available to ascertain whether indomethacin suppressed inflammation provoked by the various pathogens used in these studies. If the nonsteroidal agents can partially suppress inflammation induced by pathogenic microorganisms, the findings suggest that it may be possible to reduce inflammation without altering host resistance to infection significantly. Presumably, other defense mechanisms are able to cope with the invading pathogens, or more likely, it seems probable that some degree of inflammation occurred in all infections, regardless of the dose of indomethacin administered. Gross and microscopic inspection of the organs at the time of death support the foregoing assumption. In view of the marked function capacity of the inflammatory reaction in normal animals, one may speculate on the possibility that inflammation may be suppressed to a considerable degree without altering the capacity of the reaction to perform its function fully. This concept is not unique; there are numerous examples which illustrate the great reserve of most functions of the body. Unilateral nephrectomy or partial hepatectomy are two examples of organs carrying out their function adequately even though their capacity is reduced by more than 50%. However, if other defense mechanisms are also impaired, as observed in animals treated with large doses of

corticosteroids, then the combined adverse effects may lead to significant changes in host resistance.

In the investigations dealing with the acute bacterial infections in mice, the results of individual experiments were often quite varied, particularly during the summer months when animals were subjected to undue heat stress during shipment. Unless great care is taken to relate the cause of death to the pathogen used to induce infection, the mortality figures may be highly misleading. The varied findings appeared to be due in part to the acute, short-termed nature of these bacterial infections and to the toxicity of indomethacin at the higher dose levels. However, more often the presence of undetected latent infection interfered with the findings; this was readily demonstrated in mice treated with hydrocortisone. The present investigations also indicate that there is a great need for microbiologically defined strains of mice for studies which deal with factors affecting host resistance to infection.

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LITERATURE CITED

1. Antopol, W., S. Glauback, and H. Quittner. 1951. Experimental observations with massive doses of cortisone. Rheumatism **7**:187–196.
2. Austen, K. F. 1963. Immunological aspects of salicylate action—a review, p. 161–169. *In* A. St. J. Dixon et al. (ed.), Salicylates. J. & A. Churchill Ltd., London.
3. Berlin, B. S., G. Johnson, W. D. Hawke, and A. G. Lawrence. 1952. The occurrence of bacteremia and death in cortisone-treated mice. J. Lab. Clin. Med. **40**:82–89.
4. Clark, G. M. 1964. Indomethacin in rheumatoid arthritis. Arthritis Rheumat. **7**:300.
5. Domenjoz, R. 1960. The pharmacology of phenylbutazone analogues. Ann. N.Y. Acad. Sci. **86**:263–291.
6. Dougherty, T. F. 1947. Evaluation of alterations produced in lymphoid tissue by pituitary adrenal cortical secretion. J. Lab. Clin. Med. **32**:584–605.
7. Fauve, R. M., and C. H. Pierce-Chase. 1967. Comparative effects of corticosteroids on host resistance to infection in relation to chemical structure. J. Exptl. Med. **125**:807–821.
8. Fauve, R. M., C. H. Pierce-Chase, and R. Dubos. 1964. Corynebacterium pseudotuberculosis in mice. II. Activation of natural and experimental latent infections. J. Exptl. Med. **120**:283–304.
9. Kass, E. H., M. I. Kendrick, and M. Finland. 1953. Effect of certain corticosteroids and of growth hormone on nucleoproteins of lymph nodes. Ann. N.Y. Acad. Sci. **56**:737–741.
10. Landy, M., and L. Pillemer. 1956. Elevation of properdin levels in mice following administration of bacterial lipopolysaccharides. J. Exptl. Med. **103**:828–833.
11. Le Maistre, C., and R. Tompsett. 1952. The emergence of pseudotuberculosis in rats given cortisone. J. Exptl. Med. **95**:393–408.
12. Meier, R., W. Schuler, and P. Desaulles. 1950. On the question of the mechanism of inhibition of connective tissue growth by cortisone. Experientia **6**:469–471.
13. Robinson, H. J., H. F. Phares, H. Siegel, and O. E. Graessle. 1968. Comparative effect of indomethacin and hydrocortisone on experimental tuberculosis in mice. Am. Rev. Respirat. Diseases **97**:32–37.
14. Rowley, D. 1956. Rapidly induced changes in the level of non-specific immunity in laboratory animals. Brit. J. Exptl. Pathol. **37**:223.
15. Schechmeister, I. L., and F. L. Adler. 1953. Activation of pseudotuberculosis in mice exposed to sublethal total body radiation. J. Infect. Diseases **92**:228–239.
16. Shilo, M. 1959. Nonspecific resistance to infections. Ann. Rev. Microbiol. **13**:255–278.
17. Smyth, C. J., E. E. Velayos, and C. Amoroso. 1963. Indomethacin in acute gout using a new method of evaluating joint inflammation. Arthritis Rheumat. **6**:299.
18. Speirs, R. S. 1956. Effect of oxytetracycline upon cortisone induced pseudotuberculosis in mice. Antibiot. Chemotherapy **6**:395–399.
19. Thomas, L. 1953. The effects of cortisone in bacterial infection and intoxication, p. 147. *In* G. Shwartzman (ed.), The effect of ACTH and cortisone upon infection and resistance. Columbia University Press, New York.
20. Wanka, J., and A. St. J. Dixon. 1964. Treatment of osteoarthritis of the hip with indomethacin: a controlled clinical trial. Ann. Rheumatic Diseases **23**:288–294.
21. Winter, C. A., and E. A. Risley. 1965. Further observations on the inhibition of granuloma by indomethacin. Arzneimittel-Forsch. **15**:427–429.
22. Winter, C. A., E. A. Risley, and G. W. Nuss. 1963. Anti-inflammatory and antipyretic activities of indomethacin, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. J. Pharmacol. Exptl. Therap. **141**:369–376.