EFFECT OF CORTISONE ON EXPERIMENTAL PNEUMOCOCCAL INFECTION

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The sensitivity of an organism to infectious diseases and to intoxication, and the ultimate issue of the condition depend to a considerable extent on the normal functioning of the suprarenal glands. We have shown that the ascorbic acid content of rabbit adrenals is very considerably lowered in typhoid or pneumococcal infection. Since it is known that changes in the ascorbic acid content of the adrenals are indicative of corresponding changes in corticosteroid metabolism [3, 9], it was thought to be of interest to ascertain how the corticoadrenal hormone cortisone affects the functional state of the adrenals in infections, and what effect it has on the course of the infection.

It has been announced in a number of papers that cortisone has a beneficial effect in rheumatism [1], that it lowers the raised temperature observed in rabbits following introduction of pneumococcus [8] or typhoid [5] vaccines, and that administration of cortin has a favorable effect in certain forms of tuberculosis [2].

At the same time a number of authors have reported unfavorable effects of cortisone in experimental mycoses [11], in tuberculosis in guinea pigs [7] and in rats [4], and other conditions.

The present paper describes an investigation into the effect of cortisone on the course of pneumococcal infection and on the functional state of the adrenals, as shown by their ascorbic acid and adrenalin contents.

EXPERIMENTAL METHODS

26 rabbits of about 3 kg body weight were used in our experiments. The animals were divided into 4 groups; 9 animals were infected with pneumococcal culture, 6 were similarly infected and were treated with cortisone, 5 were not infected, but were given cortisone, and 6 served as controls.

The animals were inoculated intradermally, on the flanks, with 0.2 ml of an 18 hr culture of Type I pneumococcus diluted 5×10^{-4}. Cortisone acetate (Merck) was given by intramuscular injection, in an initial dose of 10 mg per kg body weight (the animals of the second group received their first injection simultaneously with the inoculation), followed by two doses daily of 5 mg for 2 days.

The blood adrenalin of the animals, and the adrenalin and ascorbic acid contents of their adrenals, were determined. Blood was taken from the marginal ear veins of fasting animals before inoculation or injection, 24 hr after, and then daily until death. Animals receiving cortisone alone were killed by air embolism 3 days after their first injection, and 24 hr after the last one. Animals of the control group were killed in the same way at the time of death of the inoculated rabbits.

Both adrenals were removed immediately after death, weighed, and ground with quartz sand, and protein-free extracts were prepared with the aid of 10% trichloracetic acid.

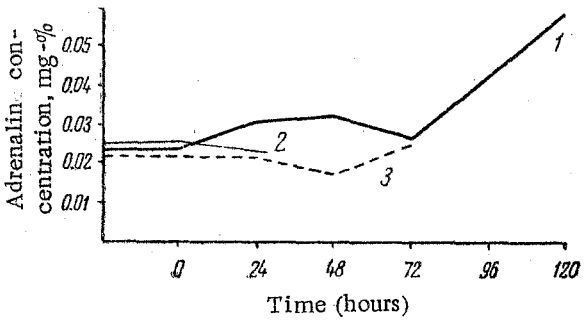
The adrenal content of the blood and the filtrates was determined by Utevskii's method, and the ascorbic acid content of the filtrates by titration with 0.02% 2, 6-dichlorophenolindophenol solution.

EXPERIMENTAL RESULTS

Our experiments showed that treatment with cortisone prevented development of local inflammatory reactions; animals not treated showed a well-marked inflammatory reaction with zones of necrosis, infiltration, and hyperemia at the inoculation sites.

Cortisone aggravated and accelerated the course of the infection, and the animals died on the second day after inoculation; those not receiving cortisone survived until the 5th or 6th day. Similar results were obtained in analogous experiments conducted by other workers in our laboratory.

Changes in blood adrenalin are represented in the graph. Curve 1 shows that pneumococcus infection causes a rise in blood adrenalin, from the normal value of 0.024 mg-% (range 0.014 to 0.030 mg-%) to a mean value of 0.044 mg-% 4 days after inoculation, and to 0.06 mg-% after 5 days (a few hours before death), i. e., the blood adrenalin content had risen 2 1/2 times higher than normal. The values for animals treated with cortisone did not exceed normal 24 hr after inoculation, although the rabbits died a few hours later (Curve 2).



Changes in blood adrenalin content after inoculation of rabbits with pneumococcus and injection of cortisone. 1) inoculation; 2) cortisone; 3) inoculation + injection.

Cortisone alone had no effect on blood adrenalin which remained at the normal level (0.022-0.026 mg-%: Curve 3) over 3 days of observation. The same applied to the control group, fed and housed under the same conditions; the values varied from 0.018 to 0.026 mg-%.

In spite of the increase in weight of the adrenals of infected animals, their adrenalin content, calculated per kg body weight, was only one-seventh that of the control rabbits (Table 1).

It is evident from the data of Table 1 that injection of cortisone into normal animals lowers the weight of their adrenals by about one third. Since their adrenalin content calculated per kg body weight remained within normal limits, but was nearly doubled per mg of gland (in connection with its fall in weight), it may be supposed that the loss in weight of the glands was suffered by their cortical parts.

There was similarly no loss of adrenalin from the adrenals of inoculated rabbits receiving cortisone (Table 1). It appears that cortisone inhibits the action on the medulla of histamine-like substances produced during the infective process, which normally cause lowering of the adrenalin content of the glands. This effect may be related to the ability of cortisone to inactivate histamine-like substances [6], by activation of enzyme systems which inactivate histamine [10].

The ascorbic acid content of the adrenals of rabbits dying of pneumococcus infection was on the average 60-75% below normal, in spite of the increase in weight of the glands (Table 2).

Cortisone caused a fall in the ascorbic acid content of the adrenals of normal animals, by about 50% per mg of gland, and, in view of the reduction in weight of the gland, by about 60-70% per kg body weight. The smaller weight of the glands was, of course, due to the depressive effect of cortisone on corticoadrenal function and on secretion of ACTH.

The ascorbic acid content of the adrenals of rabbits with pneumococcus infection treated with cortisone fell on the average by 80-85% of the normal value.

It thus appears from our experiments that cortisone aggravates the course of acute pneumococcal infection, hastens the death of the animals, and prevents development of local inflammatory reaction. At the same time it suppresses the function of the adrenal cortex, since in control animals cortisone lowers the ascorbic acid content of the glands, without affecting their adrenalin content. Cortisone treatment of pneumococcus-infected rabbits intensifies depletion of ascorbic acid, without preventing depletion of adrenalin.

TABLE 1

Change In Adrenalin Content of the Suprarenal Glands of Rabbits After Inoculation With Pneumococci And Treatment With Cortisone

Group of rabbits	No. of animals	Weight of both adrenals	Adrenalin content in μg		
			per mg of gland	in both glands	per kg body weight of animal
Normal	6	125.0 (108.4—156.5)	0.367 (0.340—0.393)	125 (100—150)	51 (32.7—70)
After cortisone	5	88.7 (68.9—111.4)	0.179 (0.423—0.900)	158.14 (150—172,8)	57.3 (47—67.4)
After inoculation with Type I pneumococcus	9	200.5 (128.1—272.4)	0.038 (0.015—0.058)	23.86 (4.93—46.75)	7.66 (2.38—14.17)
After inoculation with Type I pneumococcus and treatment with cortisone	6	117.0 (73—142)	0.380 (0.2—459)	98 (51.6—216.7)	41 (21—65.2)

Note: The figures given in Tables 1 and 2 are mean values; those in parentheses refer to range of individual variations.

TABLE 2

Change in Ascorbic Acid Content of the Suprarenal Glands of Rabbits After Inoculation With Pneumococci and Treatment With Cortisone

Group of rabbits	No. of animals	Weight of both adrenals	Adrenalin content in μg		
			per mg of gland	in both glands	per kg body weight of animal
Normal	6	125.0 (108.4—156.5)	3.5 (2.9—3.9)	1 470 (870—1 990)	488 (410—570)
After cortisone	5	88.7 (68 9—111.4)	1.87 (1.29—2.8)	419.95 (291.8—904)	150.3 (113,8—193)
After inoculation with Type I pneumococcus	9	200,5 (128.1—272.4)	0.721 (0 3—1.23)	399 (134.4—780)	135.4 (56.4—270)
After inoculation with Type I pneumococcus and treatment with cortisone	6	117.0 (73—142)	0.67 (0 57—0.81)	225.9 (154—322.4)	79.6 (46—119)

LITERATURE CITED

[1] A. L. Myasnikov, and Yu. I. Lorie, Problems of Pathology of the Cardiovascular System, Moscow, 1952, No. 2, 3-15.

[2] F. L. Elinson, Problems of Therapy of Tuberculosis, (Moscow, 1944) Vol. I, 193-203.

[3] W. M. Booker, F. M. Dent, and R. L. Hayes, et al., Proc. Soc. Exptl. Biol. Med. 78, No. 1, 170-173 (1951).

[4] M. M . Cummings, P. C. Hundgins, M. C. Whorton, and W. H. Sheldon, Ann. Rev. Tuberc., v. 65, No. 5, pp. 596-602 (1952).

[5] B. J. Duffy, and H. R. Morgan, Proc. Soc. Exptl. Biol. and Med., 1951, v. 78, No. 3, pp. 687-689.

[6] A. Goth, R. M. Allman, B. C. Merritt, and J. Holman, Proc. Soc. Exptl. Biol. and Med., 78, 3, 848-852 (1951).

[7] J. B. Jorgenson, and J. Ringsted, Acta path. et microbiol. Scandinav., 32, 4, 465-467 (1953).

[8] L. Recant, W. H. Ott, and E. E. Fischel, Proc. Soc. Exptl. Biol. and Med., 75, 1, 264-266 (1950).

[9] G. Sayers, M. A. Sayers, T. Y. Liang, and C. N. H. Long, Endocrinology, 38, 1, 1-9 (1946).

[10] D. J. Smith, Proc. Soc. Exptl. Biol. and Med., 77, 3, 534-536 (1951).

[11] Zbignien, Mankowski and Zitteton, J. Antibiotics, chemotherapy, 3, 4, 253 (1954).