THE EFFECT OF CIRCULATORY DISTURBANCES AND EDEMA OF THE LUNGS ON THE DEVELOPMENT AND COURSE OF INFECTIOUS PROCESSES (PNEUMONIA) IN THEM

COMMUNICATION II. THE EFFECT OF EDEMA OF THE LUNGS INDUCED BY THIOUREA ON THE DEVELOPMENT OF PNEUMONIA

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Many aspects of the part played by pulmonary edema in the genesis of pneumonia have not yet been explained. Some authors believe alveolar edema to be a decisive factor in the development of pneumonia [1, 7, 9, 13, 14], and certain researchers actually regard it as the initial "premicrobe" phase of pneumonia [2, 5]. Other authors hold that a condition of pulmonary edema does not necessarily lead to pneumonia [3, 6, 8]. There is very little data as to the effect of pulmonary edema on the course of pneumonia.

The contradictory nature of these opinions is to a large extent due to the difficulty of experimentally reproducing a sufficiently lasting condition of pulmonary edema. The best results have been obtained by the administration of α-naphthylthiourea, which induces a rather slowly developing pulmonary edema [10, 11, 12].

The purpose of this work was to develop a method of obtaining prolonged pulmonary edema with the aid of thiourea and to determine how this edema affects autoinfection of the respiratory organs and the development of experimental pneumococcal pneumonia.

EXPERIMENTAL METHODS AND RESULTS

Edema of the lungs was induced in 100 white rats weighing 180-200 g each by an intraperitoneal injection of an aqueous solution of thiourea.

Histological examination of the lungs was done by the usual methods.

As a rule, the development of pleural effusion and perivascular and alveolar edema was observed after the thiourea injection; less frequently, hyperemia and hemorrhages were observed in the lungs. Four degrees of pulmonary edema could be distinguished: acute, when large groups of alveoli were found filled with serous fluid, with tiny pieces of emphysematous lung tissue remaining among them; moderate, when considerable groups of alveoli containing serous fluid alternated with large zones of pneumatic tissue; mild, when serous fluid appeared only in individual alveoli or in small groups of the latter; very mild, when fluid was present in single alveoli only (Table 1).

When thiourea was injected in doses of 20 and 15 mg per 100 g animal body weight, as Table 1 shows (first and second groups), most of the rats died 3-14 hrs after the experiment began. Considerable pulmonary edema was demonstrated in the rats which were sacrificed as well as in those which died. Serous fluid was found in the lumen of the alveoli as early as an hour after the experiment began and, from this time on, was found in all the animals except those sacrificed after 24 hrs. Out of 63 animals administered a smaller dose of thiourea (10 mg/100 g), 5 died after 1½, 2, 3 (2 rats) and 12 hrs, and 58 were sacrificed – 50 during the first 48 hrs and 8 in the course of the next 3 days (see Table 1, third group).

In most of the animals which died or were sacrificed after 1½-24 hrs, fluid was present in the lumen of the alveoli. During the first 3 hrs, edema was very mild or mild and, in some rats, not even apparent. The longer the animal was alive after the injection, the more pronounced the edema until the 6th-8th hour of the experiment, when it reached its maximum degree. Thereafter, the edema gradually subsided. No pulmonary edema was observed in

TABLE 1. Changes in the Lungs of White Rats Following the Intraperitoneal Injection of Different Doses of Thiourea

Group	Thiourea dose (in mg/100 g)	Number of animals		Changes in lungs									
				hyperemia	hemorrhages	perivascular edema	alveolar edema					pneumonia	pleural effusion
							acute	moderate	mild	very mild	total animals		
First	20	Died	12	4	3	12	12	–	–	–	12	–	12
		Sacrificed	13	2	1	12	3	1	5	–	9	–	12
		Total	25	6	4	24	15	1	5	–	21	–	24
Second	15	Died	7	3	–	7	2	3	2	–	7	–	7
		Sacrificed	5	1	–	5	1	–	3	1	5	–	4
		Total	12	4	–	12	3	3	5	1	12	–	11
Third	10	Died	5	3	1	5	3	2	–	–	5	–	5
		Sacrificed	58	6	10	35	1	6	12	7	26	–	32
		Total	63	9	11	40	4	8	12	7	31	–	37

either the rats killed during the first hour or in those killed after 48 hrs. Therefore, this dose of the preparation produced a rather protracted edema of the lungs which was not, in most cases, fatal.

The development of pneumonia was not observed during either the early or the late stages. Edema of the lungs induced by thiourea does not, therefore, in itself lead to the development of autogenous pneumonia. The increase in the number of histiocytes causing some thickening of the alveolar walls which was observed at the later stages was apparently a reaction to the action of thiourea.

In the next series of experiments, we investigated the effect of pulmonary edema on the development of experimental pneumonia.

In this investigation, we used 94 white rats weighing 180-200 g each, to which an 18-20 hr bouillon culture of type III pneumococcus was administered intranasally under light ether anesthesia. Immediately after their infection, the rats were intraperitoneally injected with an aqueous solution of thiourea (10 mg/100 g). The rats were divided into three groups: the rats in the first group received 75,000,000 microbes each, the rats in the second, 30,000,000 and those in the third 1,570,000. A fourth group of experiments was performed in order to determine the effect of pulmonary edema on an existing condition of pneumonia; in these experiments, edema was induced one day after the rats were infected with pneumococcus. Rats of the same weight which did not receive the thiourea injection after the pneumococcal infection were used as the control. In addition to the usual methods of examining the lungs, we used sections stained with azan according to Heidenhain, Nicollia's carbol-thionine, Gram's method and Unna's methylene blue. The rats which had been given large doses of the microbes were examined 6, 24 and 48 hrs after the experiment began, while those which had received the lesser amounts were examined after 24, 48 and 96 hrs.

In the first group, an inflammatory process was found after 6 hrs in the lungs of both the experimental and the control animals. In the control rats, however, the foci of pneumonia were small, the process being considerably more extensive in the experimental animals. After 24 hrs, pneumonia was considerably more pronounced in the experimental animals. A marked zone of microbial edema was observed in the peripheral sections of most of the foci of the inflammation. Two of the twelve rats investigated at this time died. Progressive pneumonia was found in both of these animals, with the microbes present in almost all parts of the lungs. The foci of inflammation in the control rats were more or less leukocytic foci showing moderate microbial edema in the peripheral portions. There was less difference between the degrees of penumonia found in the two groups after 48 hrs.

In the white rats administered the smallest dose of pneumococci used in our experiments, pneumonia was found in six out of eight experimental animals, but in only two out of the eight control rats.

TABLE 2. Data on Microbial Multiplication in the Lungs of White Rats Infected with Type III Pneumococcus and Simultaneously Injected with Thiourea

	Time investigated after thiourea injection	30 min	6 hrs	24 hrs
Type III pneumococcus	Microbe coefficient	1.44	3.26	2.91

On the basis of our data, therefore, one can assume that pulmonary edema provoked by the administration of thiourea not only promotes more progressive growth of pneumonia, but also is conducive to its development.

As Harford and Hara [11] have noted, pulmonary edema ought to stimulate the development of bacterial pneumonias, due to the fact that the edematous fluid is a favorable nutient medium for microbes. Specifically, the authors indicate that microbes multiply faster under conditions of thiourea edema. We conducted bacteriological experiments to verify these data.

Using the method already described, we infected 40 rats, 20 of which were administered thiourea. All the animals were sacrificed. The animals were examined 30 min, 6 and 24 hrs after the thiourea injection. Material from the lungs was planted on a dish containing 5% blood agar. The microbe coefficient* (Table 2) was computed to facilitate analysis of the data obtained.

Table 2 shows that more microbes were obtained from the lungs of the experimental animals than from the lungs of the control rats at all the experimental intervals, including the 30 min one when no pulmonary edema had as yet developed (see above). A considerably greater number of microbes were also cultured from the lungs of the animals which had received thiourea in doses causing practically no alveolar edema (40 rats). These observations indicate the favorable conditions promoting more rapid penetration of the microbes into the lungs or their slower excretion therefrom and their increased multiplication or reduced mortality which follow the administration of thiourea to animals are not primarily due to the presence of edematous fluid in the alveoli, but are rather evoked by other factors associated with the administration of thiourea. Not being concerned in this work with other changes effected in the organism by thiourea, we present only data concerning its effect on microbial activity.

In order to study the effect of thiourea on microbes, we cultured type III pneumococcus and staphylococcus aureus on a dish containing 5% blood agar and different concentrations of thiourea (95 dishes). This investigation showed that thiourea in low concentrations (0.1-0.05 mg per dish) more than doubled the "germination" of the two cultures.

Of course, it would hardly be accurate to fully identify thiourea's effect on microbes in vitro with its effect in vivo, but the data obtained does permit the assumption that the more rapid and regular development of pneumonia observed in our experiments is evidently to be associated not so much with pulmonary edema as with the fact that thiourea affects microbes directly, reducing their mortality and possibly increasing their multiplication.

The possibility that thiourea edema affects the development of the inflammatory process is not, however, excluded by these data. As our observations show, edema developing concurrently with pneumonia undoubtedly promotes the expansion of the process through the lungs, although it is not yet clear to what extent this is due to the stimulating effect of the thiourea. A model of experimental edema with no side factors to affect microbial activity is needed to solve this question.

In the experiments in which pulmonary edema was induced the day after the animals were infected, the former had no apparent effect on the progression and expansion of the inflammatory process in the lungs. Instead, some limitation of the expansion of the pneumonia was observed. This tendency was particularly marked in the animals in which edema was most acute. Compared with that in the other experimental series, the pneumonia observed in all the animals of this series was much less pronounced. These data tally with observations we made earlier on sections [4], in which we observed limitation of pneumonia foci when the disease was associated with edema of non-microbial origin.

* The ratio of the number of viable microbes in the lungs of the experimental rats to the number of viable microbes in the lungs of the control rats.

SUMMARY

A method is presented used for inducing prolonged and usually nonfatal edema of the lungs in albino rats by intraperitoneal thiourea administration. A study was made of the effect produced by this edema on the autoinfection of respiratory organs and on the development of experimental pneumococcus pneumonia. Thiourea edema alone does not lead to pneumonia development. Experimental pneumonia was more severe which mainly depended on rapid microbial multiplication, evidently, due not to pulmonary edema, but to the fact that thiourea by itself favours microbial growth creating favorable conditions for the microorganisms. This influence of thiourea was established in vitro.

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