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ARTIFICIAL FEVER IN THE TREATMENT OF ALLERGIC DISEASES

By

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The treatment of diseases by artificially produced fever has been used for a long time in various complaints, though in modern medicine there may be a tendency to replace it by more effective drugs and other therapeutic methods. Its application in allergic diseases, and especially in bronchial asthma, is vindicated by very ancient experience, for it was Hippocrates who observed that bronchial spasm would recede during fever. Hence the saying: *febris tollit spasmum*, coined in the XIX century, which however embraced a somewhat wider range of ailments. Trousseau, who suffered himself from bronchial asthma noticed in his own case as well as in that of a patient that asthma attacks would recede during the infective bronchitis combined with high temperature. Similar observation have been frequently made in the Allergological Department in Cracow when in the patients treated for bronchial asthma notable improvement had been observed during concurrent, but unconnected diseases accompanied by high temperature.

Following our own experience as well as that described in the literature *Grabowski* (4), *Hanse* (5), *Kremer* (6), *Schubert* (7), *Weihermüller* (8) we proceeded in our clinic to treat systematically by means of artificially induced fever certain allergic diseases, mostly bronchial asthma and neurodermitis disseminata or both diseases combined.

In the years 1954-1963 in our Allergological Department

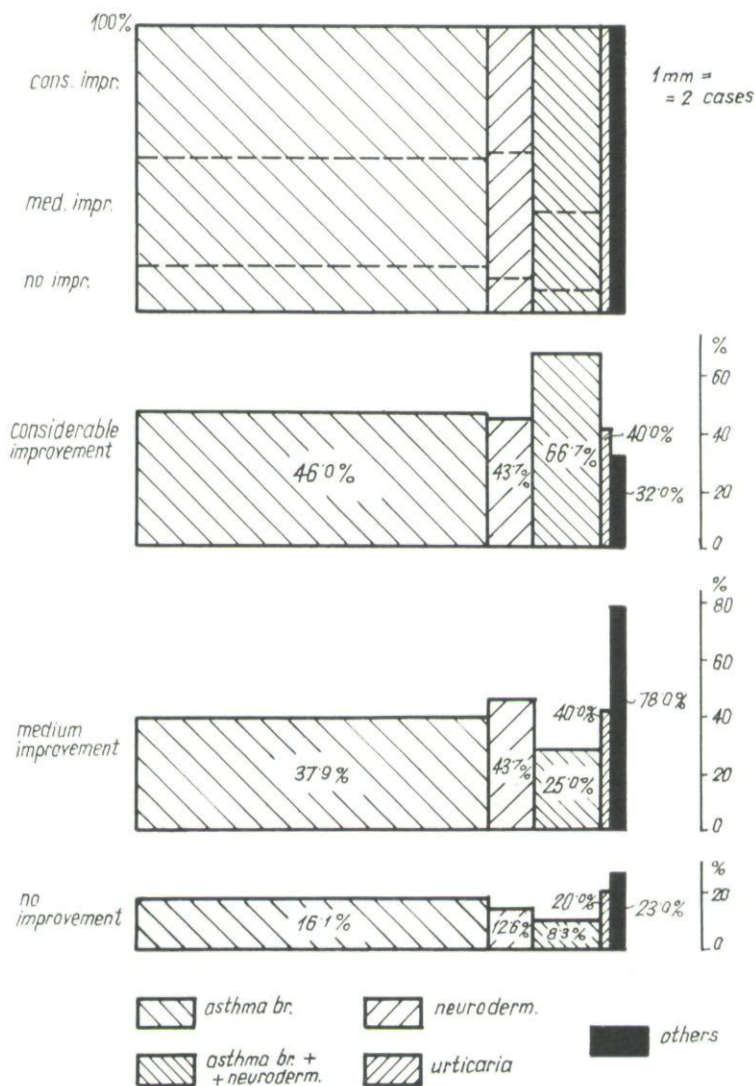
we treated by fever therapy 180 cases, 85 men and 95 women. For the treatment the cases of allergy with particularly prolonged courses and resistant to classical pharmacological methods were chosen.

Moreover, all usual medical agents were abandoned, except for bronchodilatores and expectorants, which were used only during acute attacks of asthma. The age of the patients varied between 20–50 years. The largest group were the patients with asthma bronchiale infectiosum (124 cases), next to it were the patients with neurodermitis disseminata (24 cases), and both diseases (16 cases). Apart from 5 cases where milk, therebinthin oil and peptone were used as fever inducing agents, most of the patients were treated with bacterial vaccines or pyrifex which were given intravenously every 5–6 days. In assessing the dosage, the general condition of the patient was taken into consideration as well as his reaction after the first introduction of pyrogen; some importance was also attached to the height of temperature and its duration which usually lasted from 8–12 hours. The treatment with fever was applied several times, so as to reach the total of 50–60 fever hours. In 86 cases typhoid vaccine was used, proteus vaccine in 59, pyrifex in 19, and typhoid + proteus vaccine in 11 cases.

The results of artificial fever treatment according to the particular diseases are given in Table 1. As a sign of improvement in the case of bronchial asthma we considered the interruption of a prolonged asthma bout (status asthmaticus), and also the decrease in the frequency and intensity of attacks. In addition, as objective criteria of the effectiveness of fever therapy, we accepted the enlargement of the vital capacity of the lungs, the change in the appearance of the sputum, the decrease of the number of eosinophils or their complete disappearance in the nasal secretion and sputum. Applying the above criteria to the clinical material 46 per cent of cases were assessed as showing considerable improvement, 37.9 per cent as moderate improvement, and 16.1 per cent as no improvement. As criteria of improvement in neurodermitis we

TABLE I

Results of Artificial Fever Treatment of Various Allergic Diseases.



accepted the clinically observable cessation or perceptible diminution of itching and, additionally, the decrease in the number of eosinophils in peripheral blood. The percentages are on the whole similar to those given for bronchial asthma—43.7 per cent perceptible and moderate improvement, and 12.6 per cent no improvement. For the two diseases, bronchial asthma + neurodermitis, percentages are somewhat higher 66.7 per cent perceptible improvement, 25.0 per cent moderate improvement, and in 8.3 per cent of cases no improvement.

In the cases of urticaria and oedema Quincke as sign of improvement we accepted the disappearance or diminution of skin weals. In rhinitis allergica the cessation of sneezing and the disappearance or diminution of nasal secretion as well as the disappearance of eosinophils in the secretion of the nasopharyngs.

In chronic eczema the measure of improvement consisted in the diminution of pruritus, and the absence of new eruption.

In view of the small number of the latter cases urticaria, rhinitis, eczema their percentages are not comparable with the data given above.

In Table 2 results of treatment with artificial fever are given according to the type of pyrogen used. When using typhoid vaccine marked improvement was obtained in 46.5 per cent cases, moderate improvement in 39.5 per cent, while for proteus vaccine corresponding figures were 49.2 per cent and 37.3 per cent respectively. The results obtained in the case of other agents used (pyrifer, typhoid vaccine + proteus vaccine) are difficult to assess numerically on account of the small number of cases. But the above data are sufficient to draw the conclusion that the success in treatment with artificially induced fever is independent of the type of pyrogen used. It should be, however, observed, that after the use of the typhoid vaccine and pyrifer the state of high temperature of the body lasted longer and general reactions such as headache, muscular pain were more pronounced than with the proteus vaccine.

TABLE 2

Results of Artificial Fever Treatment According to the Pyrogen Applied.

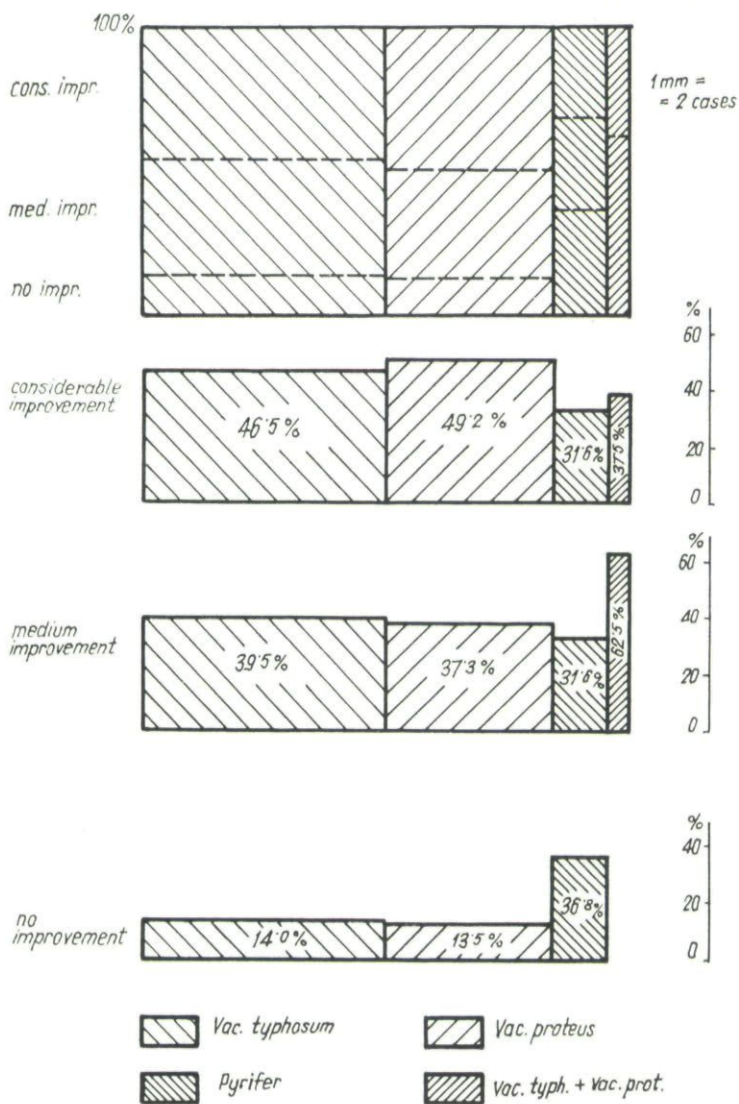
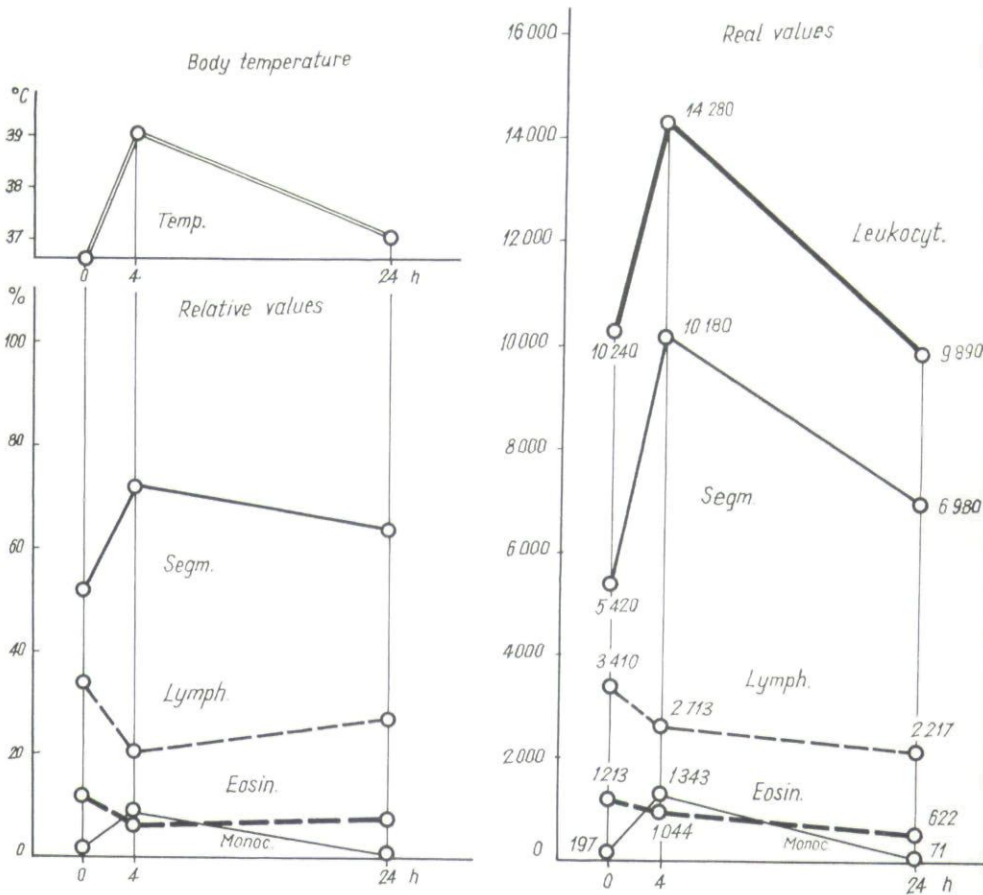


TABLE 3
Reactions of Leukocytosis and White Blood Cells in Artificial Fever Treatment.



In the course of treatment with artificially induced fever the behaviour of leukocytes was studied in terms of their actual number as well as their percentage value. The observations were made before breakfast before the actual introduction of the vaccine, as well as four and twenty four hours after its introduction. The data, based on 120 cases investigated, are given in Table 3.

It should be noted that there is an initial leukocytosis (aver-

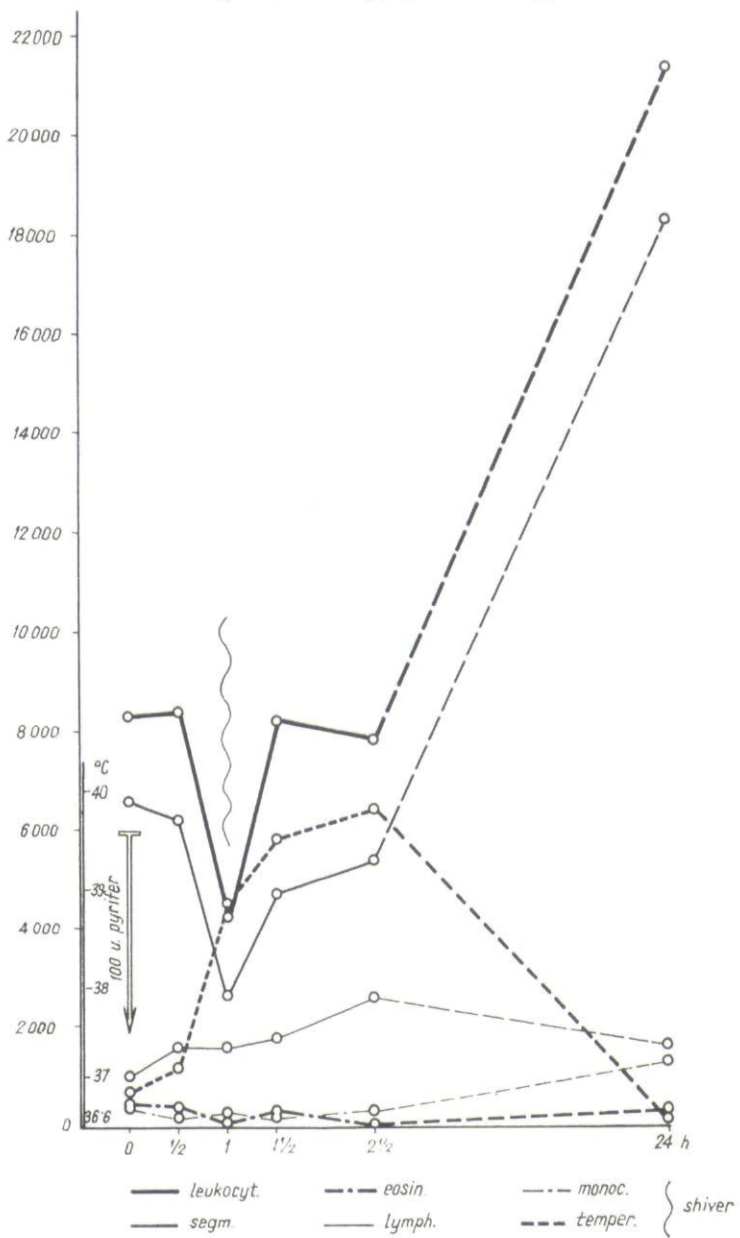
age 10,240) which in this case is accounted for by the type of diseases (asthma bronchiale infectiosum, neurodermitis diss). A higher lymphocytosis and eosinophilia are also connected with the allergic nature of disease. Also, as can be seen from Table 3 four hours after the introduction of the fever agent into the veins, when the rigor has finished, and the temperature rises, the leukocytosis markedly increased (average 14,280), after twenty four hours, when the temperature returned to normal, to fall somewhat below the initial (average 9,890). It was also found that the increased number of neutrophils during the period of high temperature was accompanied by a considerable decrease in the number of lymphocytes and eosinophils while the number of monocytes maintained its high level. After 24 hours the number of segmented leukocytes somewhat fell at the expense of a slight rise of the amount of lymphocytes and eosinophils with monocytes again falling.

In order to make a more detailed study of the behaviour of individual leukocytic elements expressed in their proportional composition additional investigations were conducted in the case of eight patients with bronchial asthma. They consisted in blood tests carried out every half an hour from the moment of the intravenous introduction of pyrogen to the onset of rigors and the rise of temperature. It should be added that for the sake of clearness of the picture only pyrifera was used in those tests.

It was found that after the introduction of pyrifera the white cell count diminished, being lowest during the rigor, and afterwards began to rise rapidly which was parallel with the increase of the body temperature. At first an initial decrease of the number of all types of leukocytes was seen, but especially of the neutrophils where the decrease was greatest. When after the chill the temperature rose, a great increase of segmented neutrophils was observed (Table 4).

Our results, therefore, agree with the experimental findings of *Barry Wood* (1). *Besson* (2) discovered the presence of a pyrogenic substance in leukocytes which, when introduced

TABLE 4
*Body Temperature, Leukocytosis and the Percentage of the White Blood Cells
 During Fever Therapy (a Case Study).*



intravenously, after a few minutes produced fever with accompanying leukocytopenia. The origin of the leukopenia Beson tried to explain by the process of liberation of termolabile pyrogen from the leukocytes.

Our examinations of the skin exudate (skin window technique) (9), carried out with 6 bronchial asthma patients and 2 patients with bronchial asthma + neurodermitis during the pyrogen induced fever reaction, have shown, apart from a marked decrease of the number of eosinophils, a considerable rise of neutrophiles.

The actual mechanism of benefit of fever therapy in allergic diseases consists most likely in the stimulating effects which it has on the function of the suprarenal cortex (3). It will be remembered that in the early stages of steroid therapy it was discovered that the most characteristic manifestation was the disappearance of eosinophils from peripheral blood (Thorn's test).

Similar phenomenon was observed in our Department during fever treatment. The problem has been studied in some detail by dr J. Illg¹ of our Clinic who found a markedly increased secretion of endogenic steroids in the urine during the pyrifert treatment of the cases of bronchial asthma.

CONCLUSIONS

As a result of investigations the following conclusions have been reached:

1. Fever therapy induces a definite, though not a lasting improvement in such allergic diseases as bronchial asthma, neurodermitis or both.
2. The therapeutic result does not depend on the type of pyrogen used, but on the duration of fever.
3. It would seem that in order to obtain the maximum possible therapeutic effect of fever treatment the total of fever hours should approximaely amount to 60 hours.

¹ In a paper to be published.

4. The mechanism of action of fever seems to consist of a stimulation of the suprarenal cortex. This seems to find its corroboration in the characteristic behaviour of the eosinophils in the percentage values of the peripheral blood, in the skin exudate, and finally in an increased excretion of ketosteroids.

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