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Swedish National Association against Tuberculosis. Therapeutic Trials Committee (1950). Para-aminosalicylic acid treatment in pulmonary tuberculosis. *American Review of Tuberculosis* 61:597-612.

Key passages

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PARA-AMINOSALICYLIC ACID TREATMENT IN PULMONARY TUBERCULOSIS

Comparison between 94 Treated and 82 Untreated Cases

THE THERAPEUTIC TRIALS COMMITTEE OF THE SWEDISH NATIONAL
ASSOCIATION AGAINST TUBERCULOSIS¹

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INTRODUCTION

In 1943, on the basis of studies made by Bernheim (1), Lehmann (2), and Rosdahl (3), investigations on para-aminosalicylic acid (Aminosalylum, PAS) were started, and soon after the production of PAS was begun at Ferrosan Research Laboratories in Malmö, Sweden. Clinical tests with PAS in treatment of pulmonary tuberculosis were started in March 1944 at the Renström Hospital in Gothenburg (Vallentin (4), Lehmann *et al.* (2b and 12)), and later in many other hospitals (Westergren (5), Stavenow (6), Alin and Difs (7), Carstensen and Sjölin (8), Dempsey and Logg (9), Erdei (10), Steinlin and Wilhelmi (11), and others). The largest study, 378 cases from six Swedish sanatoriums, has been reported by Vallentin, Törnell, Beskow, Carstensen, Thune, Helleberg, and Lehmann (12). Distinct clinical improvement after PAS treatment was noted in so great a percentage of the cases that para-aminosalicylic acid could be assumed to have some value as a remedy against tuberculosis. The account published of these investigations affords no direct information, however, as to how large a part of the noted improvement could be ascribed to PAS, and how large a part was due to other treatment given at the same time (sanatorium regimen, *et cetera*). Hence it was considered necessary to start an investigation in which a group of PAS-treated cases should be compared with a control group not given PAS but in all other respects treated in exactly the same way as the PAS group.

¹ The Committee for the Trial of Para-aminosalicylic Acid has the following members: C. Sigurd Backman (Head of Sjö-Gunnarsbo Sanatorium, Åsunden); Gösta Birath (Head of Tuberculosis Department II, Söderby Sjukhus, Uttran; Assistant Professor of Phthysiology, Karolinska Institutet, Stockholm); Torsten Bruce (Head of Tuberculosis Department I, Söderby Sjukhus, Uttran; Assistant Professor of Medicine, Karolinska Institutet, Stockholm); Leonard Goldberg (Associate Professor of Pharmacology, Karolinska Institutet, Stockholm); Bertil Karth (Head of Central Sanatorium, Västerås); Rolf Lemming (Head of Central Sanatorium, Arvika); Gunnar Lindgren (Head of Remedy Section, Royal Medical Board; Assistant Professor of Medicine, Medical Service, Serafimerlasarettet, Stockholm); and John Lundquist (Head of Tuberculosis Section, Royal Medical Board; General Secretary of the Swedish National Association against Tuberculosis).

METHOD

The investigation has been carried out in five Swedish sanatoriums. As soon as a patient was admitted, it was decided whether the case was suitable for testing the efficiency of PAS. One-half of the patients in this category were treated with PAS, and the other half were used as controls, the distribution of the cases on these two groups being determined by allotment.

All cases of miliary tuberculosis or tuberculous meningitis received streptomycin and were excluded from the study. Moreover, all patients with clinical symptoms of tuberculosis of the small intestine were excluded from the trial and the allotment, and were treated with PAS as soon as they had been admitted (8).

The physician in charge was not told whether a case was to be given PAS or would belong to the controls, and a placebo of the same appearance, smell, and acid taste as PAS granulate was distributed to the patients of the control group.

TABLE 1
Length of Test Period

GROUP	TEST PERIOD (WEEKS)								MORTALITY		TOTAL NUMBER OF CASES
	1-2	3-4	5-6	7-8	9-10	11-12	13-14	≥ 15	Absolute number	Per cent	
Number of cases treated with PAS		3	1			5		85	3	3.2	94
Number of controls		3	5	3		2		69	9	11.0	82

Three patients were discharged after a little more than two months' treatment, by their own request and against advice; two after 2.5 months on account of lack of accommodation. In 3 cases showing a very rapid deterioration, it was considered necessary to discontinue the trial after six weeks of test period and to change to another therapy. When computing the material it was found that all these 3 cases belonged to the controls. One case was given PAS for only two months, another for only one month, a pronounced alimentary discomfort caused by PAS having made it impossible to fulfill the treatment for three months. Twelve patients died during the test period. The difference, 7.8 ± 3.90 per cent, in the mortality between the PAS-treated cases and the controls is on the border of significance.

The PAS granulate² contained 70 per cent para-aminosalicylic acid and was varnished with shellac. This coating protects the material from the gastric juice for at least 30 minutes.

A total daily dose of 10 Gm. of para-aminosalicylic acid was given in individual doses of 5, 2, 2, and 5 Gm. of the granulate, administered with meals. For children the dose was decreased in proportion to weight. The chemotherapy was continued for a total period of three months. In a few cases (12 per cent of the total number), however, the treatment had to be discontinued earlier (table 1).

Before starting treatment, a detailed examination of each patient was carried out, including temperature and weight determinations, chest roentgenograms, erythrocyte sedimentation rates, differential leukocyte counts, measurements of sputum volume, and search for tubercle bacilli in smears of sputum.

² Manufactured by Ferrosan Ltd., Malmö, Sweden.

During the test period, roentgenograms were taken once a month and the sputum volume was measured daily. The other examinations were repeated at intervals of no longer than 14 days.

Statistical Methods

$$\sigma = \text{standard deviation} = \sqrt{\frac{\sum(x - \bar{x})^2}{n - 1}} \quad (1)$$

$$\text{Standard error } (\mathfrak{E}_M) \text{ of mean } (M): \mathfrak{E}_M = \frac{\sigma}{\sqrt{n}} \quad (2)$$

n = number of variates

$S(\)$ = sum of . . .

x = variate

$$\bar{x} = \text{average of variates} = \frac{S(x)}{n}$$

$$\text{Standard error of difference } (\mathfrak{E}_\Delta) \text{ between means } (M_1, M_2) = \mathfrak{E}_\Delta = \sqrt{\mathfrak{E}_{M_1}^2 + \mathfrak{E}_{M_2}^2} \quad (3)$$

Significance is tested by using Student's t with the appropriate number of degrees of freedom according to ordinary formulas (13).

X-value: Comparison of two series of means, i.e., a sequence of means from the control group ($M_1, M_2 \dots$) and a sequence of means from the PAS group ($M_1'', M_2'' \dots$), was performed in the following way:

The differences ($\Delta_1, \Delta_2, \dots$) between corresponding means from each series ($\Delta_1 = M_1 - M_1''; \Delta_2 = M_2 - M_2'' \dots$) were computed, the corresponding t -values of the differences ($t_{\Delta_1} = \frac{\Delta_1}{\mathfrak{E}_{\Delta_1}}; t_{\Delta_2} = \frac{\Delta_2}{\mathfrak{E}_{\Delta_2}} \dots$) were added, and were divided by \sqrt{N} , where N is the number of differences $\Delta_1, \Delta_2 \dots \Delta_N$.

The resulting value, denoted by X , will approximately be normally distributed (14) with the standard deviation 1. Its significance is tested as an ordinary Student's t with an infinite number of degrees of freedom under the assumption that the differences ($\Delta_1, \Delta_2 \dots$) are distributed at random.

Computation of rectilinear regression line, regression coefficient, analysis of covariance, et cetera, were performed according to ordinary formulas (13, 15).

$$\text{Standard error of percentage } \mathfrak{E}_p = \sqrt{\frac{p(100 - p)}{n}} \quad (4)$$

$$\text{Standard error of difference between two percentages } \mathfrak{E}_{P_1 P_2} = \sqrt{\mathfrak{E}_{P_1}^2 + \mathfrak{E}_{P_2}^2} \quad (5)$$

Significance tested by Student's t for an infinite number of degrees of freedom ($n > 50$).

Comparison of percentages ($n < 50$), tests of homogeneity and heterogeneity, agreement between distributions, et cetera, were performed by χ^2 - analysis according to ordinary formulas (13).

Levels of significance (in accordance with Cramér):

The 5 per cent level ($P = 0.05 - 0.01$) = almost significant

1 per cent ($P = 0.01 - 0.001$) = significant

0.1 per cent ($P < 0.001$) = highly significant.

CLINICAL MATERIAL

The distribution of the material according to types of tuberculosis is given in figure 1 and according to sex and age in figure 2. As expected, the distributions in the PAS and the control group are in good agreement, the random probability being > 0.3 .