The Treatment of Tuberculosis in Sweden with Para-Aminosalicylic Acid (PAS): A Review

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Historial Remarks

The tuuberculostatic effect of PAS was discovered by the writer in 1943.[1-3] On the basis of the studies of F. Bernheim on the stim ulating effect of benzoic and salicylic acids on the respiration of the tubercle bacillus, it was suggested that the introduction of an aminogroup in the salicylic acid molecule in para-position (4-position) should be able to convert the stimulating effect into an inhibitory effect and thereby inhibit even the growth of the bacillus. PAS was synthesized by K. G. Rosdahl at the Ferrosan Company in Malmo, Sweden, in December 1943 and the tuberculostatic effect demonstrated in vitro in the same month.

The first clinical trials were conducted by Dr. G. Vallentin and the writer at Renstroms sanatorium in Gothenburg in March 1944, thus about half a year before the first clinical trials with streptomycin in the United States.

PAS was first used in the local treatment of Monaldi fistulas and abscesses, then in hopeless cases of pulmonary tuberculosis and later on in moderate and slight cases (Lehmann[1] and Vallentin[4]). During the following years the Ferrosan Company produced larger quantities of PAS and a team work on the treatment of pulmonary tuberculosis in six Swedish sanatoria was established. A report on this work—378 cases—was presented at the conference of the Scandinavian Tuberculosis Association in Copenhagen in 1948. (Vallentin, Tornell, Beskow, Carstensen, Thune, Helleberg and Lehmann[5]).

Chemical Properties, Absorption, Excretion and Toxicity of PAS

PAS is an acid of about the same strength as benzoic acid. It is soluble in water only to 0.2 per cent. The sodium salt is however soluble to about 96 per cent (Rosdahl[6]). The solubility decreases with decreasing pH. These data are of interest for the absorption of PAS: because of the slight solubility in acid solution it will only to a slight extent be absorbed in the stomach. When successively neutralized in the intestines PAS is dissolved and absorbed. PAS is a small molecule and is quickly absorbed and

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excreted. A peroral dose of 4 g. of the acid will be excreted within three to four hours, the sodium salt somewhat quicker.

The blood concentration is naturally dependent on the speed of absorption and the speed of excretion and will have its maximum after ½ to 1 hour. In order to delay the absorption of PAS the Sewdish preparation of PAS* is enteric coated in small granules first dissolving in the small intestines. With this preparation the blood will show maximum values first after about two hours and after five to six hours a single dose of four grams is excreted in the urine. Repeated doses with an interval of three to five hours is required for a permanent blood concentration.

High concentrations of PAS are achieved in the kidney and the urine. A daily dose of 14 grams PAS granules (11 grams PAS*) will give a concentration of 300 to 900 mg. per cent in the 24 hours urine. As such high concentrations are not necessary for the treatment of tuberculosis of the kidney and urinary tract the treatment of these forms of tuberculosis can be done with a lower dose (8 to 10 grams granules).

About half of the PAS in the urine is found in the acetylated form which is not tuberculostatic. The PAS not excreted is mainly found in the tissues rich in elastin (Alin and Helander[7]). Due to the high solubility of the PAS in the urine no deposits of PAS are seen in the kidney or urine even after the highest dosage of PAS (20 to 30 gm. sodium-PAS per day). See also Alin and Difs.[8]

As to the *toxicity* of PAS no damage of the liver, heart or kidney have been seen. Intestinal complaints in the form of nausea, vomiting and diarrhea was frequently seen before a suitable coating substance was found. Still some sensitive patients react in this way. However, after a free interval of four to six days the drug is often tolerated well.

Administration of PAS

Different forms of administration of PAS have been tried: Permanent *intravenous* infusions (2 per cent) in most cases give rise to trombophlebitis within three to four days. This experience was won with rather impure preparations and possibly the more pure preparations of recent years are better tolerated. *Intramuscular* injections have to be given in large repeated doses (10 ml., 10 per cent solution) in order to provide permanent blood concentrations. As they are rather painful and PAS is too quickly absorbed and excreted, this form of administration cannot be recommended. The *peroral* administration is to be used as the routine method.

*The granules contain 30 per cent coating substances. Special measures have been used containing ca. 2.2 grams of the granules. That is why the doses refer to the granules. In the future measures containing 2 grams of the acid will be used.—The Ferrosan LTD. Malmo 3. Sweden.

Intestinal complaints can be treated with interruption of the administration or a few drops of opiate or a teaspoonful of magnesium oxide before PAS is given. *PAS should always be given together with or after a meal* or a glass of milk and some bread and butter. The granules or dragées should not be chewed.

Intralumbar injections of 5 to 10 per cent sodium PAS solutions have been used in cases of meningitis (two times a week in the beginning of the disease). After a few weeks treatment the viscosity of the cerebrospinal fluid increases and makes aspiration impossible—if due to the disease or the injections has not been recognized.

Intrapleural injections have been used in the treatment of empyema. During the first year 200 to 300 ml. 5 per cent solutions were used but later on only 20 to 25 ml. 10 to 20 per cent solutions were injected after aspiration once a week according to Dempsey and Logg.[9]

For the *local application* of PAS solutions in the treatment of skin-tuberculosis (lupus), fistulas and abscesses 5 to 10 per cent solutions have been used. For the use in fistulas and abscesses the viscosity of the solutions was increased as desired by addition of 1 to 2.5 per cent cellugelphosphate. PAS in ointments has not been effective (Lemming[10]).

Pulmonary Tuberculosis: A Comparison with Streptomycin

The greatest experience of the treatment with PAS has been gained in pulmonary tuberculosis. In the following an attempt is made to compare the efficacy of PAS as evidenced from the above mentioned team work of six Swedish sanatoria (Vallentin, Tornell, Beskow, Carstensen, Thune, Helleberg and Lehmann[5]) with that of streptomycin as presented by the Army, Navy and Veterans Administration in the *American Review of Tuberculosis,* 56:485, 1947.

The PAS material consisted of 378 cases of pulmonary tuberculosis. Certain rules were established for the selection of the cases and the treatment. The rules were the following:

1) The diagnosis should be made by a positive culture or guinea pig test just before the treatment or by a typical x-ray together with a positive slide.

2) The pulmonary process should be progressive or stationary for some months without signs of regression.

3) Preferably far advanced and moderate cases of exudative as well as proliferative types with or without other complicating localizations of tuberculosis should be treated.

4) The observation time before treatment should be at least two months with rest in bed and ordinary sanatorium regime.

5) Cases treated with collapse therapy were included in the material and not considered to interfere with the estimation of the PAS effect, if the collapse therapy had been finished three months before the PAS treatment was commenced or the collapse therapy had been instituted three months before PAS and the process still showed signs of progression. The collapse therapy should be continued during the treatment as before PAS. No form of collapse therapy should be introduced during the PAS treatment or during the observation time after PAS.

6) The age of the patients should be between 15 and 60 years, preferably between 15 and 35 years.

7) PAS should be given orally with an average dose of 14 gms. a day divided into four to six doses. The treatment should be continued at least during one month and if possible without interruption.

8) The observation time after PAS should be at least three months.

9) Certain rules were established for laboratory procedures including erythrocyte sedimentation rate once a week, hemoglobin and count of the white cells every 14 days and sputum examinations and x-ray every month. The patients were weighed once a week or once fortnightly.

TABLE 1

Clinical Material

	SEX				AGE IN YEARS					
	Male		Female		5-15 0 - 0		15-35 18-30		35 31-50	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
PAS material	99	(48.3)	106	(51.7)	6	(2.9)	151	(73.7)	48	(23.4)
Streptomycin material	219	(98.2)	4	(1.8)	0	(0)	161	(72.2)	62	(27.8)

	Extent of Lesion						Predominant Type of Lesion			
	Minimum		Moderate		Far. Adv.		Exudative		Proliferative	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
PAS material	10	(5)	41	(20)	154	(75)	122	(59.5)	83	(40.5)
Streptomycin material	2	(0.9)	65	(29.1)	156	(70)	83	(63.4)	48	(36.6)

	CAVITIES				COURSE OF DISEASE			
	Present		Not Present		Progressive		Stationary	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
PAS material	169	(82.4)	436	(17.6)	184	(89.7)	39	(10.3)
Streptomycin material	182	(81.6)	41	(18.4)	122	(85.5)	19	(14.5)

The experience was soon gained that it was not always possible to maintain an observation time of two months before the treatment with PAS. Rapid deterioration of the patient during the observation time as well as the claims of the patients or their relatives called for earlier treatment. The rules established were fulfilled in only 205 cases. This "selected material" is therefore best adapted for elucidating the therapeutic effect of PAS. No collapse therapy was thus *instituted* during the observation time before the PAS treatment, during the treatment or during the after-observation time.

The streptomycin material included 223 cases. Collapse therapy was in this material used in some cases during chemotherapy when a contralateral spread appeared or during the afterobservation time if it was found "essential" to the patient. No figure is given of the frequency of such collapse therapy. It is therefore ques-

TABLE 2

Frequency of Complicating Tuberculous Localizations in Pulmonary Tuberculosis. Total material, 378 cases; Selected material, 205 cases.

	Total Number		Selected Material	
	No.	Pct.	No.	Pct.
Tuberculous laryngis	9	(2.4)	7	(3.4)
Tuberculous tracheobronchial	35	(9.0)	30	(14.6)
Pleurit, exs.	18	(5.0)	7	(3.4)
Empyema pleurae	29	(7.7)	22	(10.7)
Tuberculous intest.	55	(14.5)	49	(23.9)
Tuberculous urogenital.	10	(2.7)	8	(4.0)
Tuberculous lymfoglandul.	8	(2.1)	7	(3.4)
Tuberculous ossium and art.	5	(1.3)	3	(1.5)
Tuberculous miliary	4	(1.1)	4	(2.0)
Tuberculous pericarditis	2	(0.5)	1	(0.5)

TABLE 3

Treatment

Duration of PAS Treatment, in Months

	1		1 to 3		3 to 6		6	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
PAS material	0	(0)	62	(33.3)	100	(48.8)	43	(20.9)
Streptomycin material:	Four months' treatment. Daily dose generally 1.8 gm.							

tionable whether the streptomycin material should be compared with the "total" PAS material or the "selected." However to exclude too many interfering undefined factors from the PAS material, the "selected" has been chosen for the comparison. In order to compare it with the streptomycin material it was necessary to rearrange the material according to the American classifications. However, some of the grouping differed too much in the two materials to allow a direct comparison and the evaluation of the treatments have to be described for each material.

When reviewing the two *clinical materials* (Table 1) it is astonishing to find that they are comparable in many respects: age of patients, character of the pulmonary processes, frequency of cavities and so on. The observation time before treatment is two months in both materials. The impression has, however, been gained that the cases in the "far advanced" group in the PAS material are more severe than in the streptomycin material. This is evidenced by the high frequency of complicating localizations of tuberculosis—especially that of intestinal tuberculosis (Table 2). Thus there should not be expected as good results in the PAS material as in the streptomycin material.

The treatment with streptomycin was fixed to four months whereas the PAS treatment was adjusted according to the individual cases. As seen from Table 3 the PAS treatment was three to six months in 49 per cent—thus of a similar duration as in the streptomycin material. In 30 per cent the PAS treatment was one to three months and in 21 per cent more than six months.

In spite of the differences in the duration of the treatment the comparison of the efficacy of the two drugs seems justified, as the majority of the cases in the streptomycin material—about 80 per cent—had developed resistance to the drug within three to four months treatment. Therefore, only in a minor number of the cases further improvement could be expected to take place by continued treatment.

In the treatment with PAS the problem of bacillary resistance is of less clinical importance as, to our present experience, it develops in a minor part of the cases, is less pronounced and coming first after three to five months treatment (Lehmann[11]). Some cases have been treated one to two years without developing resistance. However, even in a minor part of this material better results could possibly have been attained, as part of the cases were not adequately treated due to lack of PAS during the first year. Summing up, it seems as if the two materials to the same degree will present results indicating what can be achieved by the two drugs.

As to the *clinical observations during treatment* the PAS mater-

ial shows better results in *temperature and sedimentation rate* (Table 4).

Normal temperature was attained in 75 per cent with PAS, in 47 per cent with streptomycin. A "decrease" in E.S.R. was observed in 84 per cent with PAS, in 30 per cent to normal values, whereas a "decrease" in the streptomycin material was registered only in

TABLE 4

Clinical Observations During PAS Treatment

	TEMPERATURE				GAIN IN WEIGHT	
	Afebrile throughout	Decrease to normal	No decrease to normal	Unaffected	1 kg or more for the PAS material
	No. Pct.	No. Pct.	No. Pct.	No. Pct.	No. Pct.
PAS material	53 (25.9)	114 (75)	19 (12.5)	19 (12.5)	127 (61.9)
Streptomycin material	63 (28.2)	76 (47.5)	41 (25.6)	43 (26.9)	188 (84.3)

	ERYTHROCYTE SEDIMENTATION RATE		
	Normal throughout	Decrease	Unaffected
	No. Pct.	No. Pct.	No. Pct.
PAS material	10 (4.9)	161 (83.7)	34 (16.3)
Streptomycin material	39 (17.5)	94 (51.1)	90 (48.9)

	SPUTUM		BACILLI IN SPUTUM OR LAVAGE			
	Not present	Disappearance or decrease	Not present before treatment		Present before Treatment	
			Continued negative	Changed positive	Changed negative	Continued positive
	No. Pct.	No. Pct.	No. Pct.	No. Pct.	No. Pct.	No. Pct.
PAS material	18 (8.8)	132 (70.5)	0 (0)	0 (0)	58 (28.2)	147 (71.8)
Streptomycin material	? (?)	178 (79.8)	? (?)	? (?)	82 (43.0)	108 (57.0)

	X-RAY OBSERVATIONS. PARENCHYMATOUS INFILTRATIONS				
	Complete regression	Marked regression	Moder. or slight regr.	Unchanged	Progress. or new infiltr.
	No. Pct.	No. Pct.	No. Pct.	No. Pct.	No. Pct.
PAS material	0 (0)	73 (35.5)	60 (29.3)	56 (27.3)	16 (7.8)
Streptomycin material	6 (2.8)	123 (56.9)	54 (25.0)	14 (6.5)	19 (8.8)

	X-RAY OBSERVATIONS. CAVITIES			
	Closed or lost to view	Smaller	Unchanged	Larger or develop. during treatment
	No. Pct.	No. Pct.	No. Pct.	No. Pct.
PAS material	31 (18.3)	46 (27.2)	80 (47.3)	12 (7.2)
Streptomycin material	47 (25.8)	67 (36.8)	68 (37.4)	0 (0)

51 per cent. The *gain in weight* was superior in the streptomycin material, 84 per cent compared with 62 per cent for PAS. However, it is not mentioned how large the gain in weight should be in the streptomycin material to be registered. In the PAS material it was at least one kg.

Concerning observations in *sputum decrease* and *sputum conversion* the streptomycin material is superior. Sputum decrease was observed in 79 per cent as compared with 70 per cent for PAS. Still more striking is the difference in sputum conversion: 43 per cent and 28 per cent respectively. However, here the frequency of the severe cases in the PAS material with old cavities and processes of proliferative type has to be considered. In the less severe "total" PAS material the conversion of sputum was 43 per cent. To some part these better results in the streptomycin material are assumingly due to the use of collapse therapy in this material.

Regressions of *parenchymatious infiltrations* and *cavities* are difficult to compare in the two materials as the figures for the streptomycin material only refers to lesions of the exudative type whereas the PAS material refers to both lesions of exudative and proliferative nature and these were of about the same frequency. Even the classifications of the regressions were different in the two materials. More comparable is the frequency of "progressions or new lesions" during treatment and this is 7.8 per cent for PAS and 8.8 per cent for streptomycin. When studying the streptomycin paper and comparing the different reports with the PAS material it seems, however, as if streptomycin gives somewhat faster and more complete regressions of the infiltrations than PAS. Further studies on more comparable materials, or with more comparable registrations, are necessary for definite conclusions.

Concerning changes in cavities in the two groups there are not too marked differences. "Closure or lost to view" dominates with 23.8 per cent in the streptomycin material as compared with 18.3 per cent in the PAS material.

TABLE 5

After Treatment Observations. Observation Time 3 Months or More

	Improvement continued No. Pct.	Improvement stationary No. Pct.	Worse No. Pct.	Dead. during treat. or after observ. time No. Pct.
PAS material	30 (57.6)	7 (13.5)	7 (13.5)	8 (15.4)
Streptomycin material	77 (34.5)	86 (38.5)	32 (16.4)	? (?)

FIGURE 1 FIGURE 2 FIGURE 3

Fig. 1: A man of 62 years. Onset of disease November 1948. Fever, sedimentation rate 50mm/one hour/Westergren, sputum positive, weight 66 kg. X-ray just before treatment December 27, 1948: Right hilus enlarged with a walnut sized ring formed shadow. Scattered infiltrations of the lung field with another walnut sized thin walled ring shadow medial at the right of the clavicle.—*Fig. 2:* The same case on January 28, 1949 after one months treatment with 14 grams PAS granules a day. Normal temperature, sedimentation rate, 6 mm./one hour. Clearing of the infiltrative lesions in the lung field and of the walls of the cavities. Shrinking of cavities.—*Fig. 3:* Same on June 28, 1949 after continued PAS therapy for six months. Cavities lost to view and lung fields nearly cleared of infiltrations. Sputum negative on guinea pig innoculation. Left hospital June 30, 1949 with a gain in weight of 10 kg.

As an illustration of the changes seen on the x-ray films, two cases should be mentioned (See Figures 1-6).

In the *after-treatment observations* (Table 5) the PAS material predominates with a much higher frequency of *continued improvement*—the figures are 58 per cent to 35 per cent for streptomycin. This could possibly be expected as the majority of the bacilli during the streptomycin treatment develope resistance to the drug, whereas this is not the case with PAS. Naturally differences in the judgment of the cases can be responsible to some extent for the different figures.

As to the *deaths,* the frequency in the PAS material is 15.5 per cent. In the single reports on the streptomycin treatment deaths are mentioned, but the total is not given in the leading article.

Recently Bachman, Birath, Karth, Lemming, Lindgren and Lundquist presented another team work on pulmonary tuberculosis.[12]

When comparing PAS and streptomycin attention has to be paid to other properties of the two drugs which have not been registered in the tables, and these are:

1) The frequency with which drug resistance is developed during treatment.
2) The mode of administration, and
3) The toxicity of the drugs.

The daily intramuscular injections of streptomycin is a draw back for this treatment and still more this is the case with the toxic reactions involving the nervous system, which restricts the use of streptomycin in minimal lesions, thus just in those phases of the disease, in which a chemotherapeutic agent has the greatest possibilities. There was a high frequency of drug resistance in the treatment with streptomycin—in 80 per cent of the cases the bacilli were found resistant after three months treatment. With PAS we have only found a slight resistance in a minor part of the cases and it is developed only after several months of treatment.

As a *general conclusion* of this comparison between the two drugs, it must be said that their effect on the symptoms are somewhat different, the streptomycin appearing to dominate in the x-ray findings whereas PAS dominates in its effects on temperature and sedimentation rate and seems to give more stable after-treatment results. The lack of toxemic reactions when using PAS as compared with streptomycin is to the benefit of the former drug and allows us for the first time to treat even early and slight cases of all forms of tuberculosis chemotherapeutically, possibly even out-door patients.

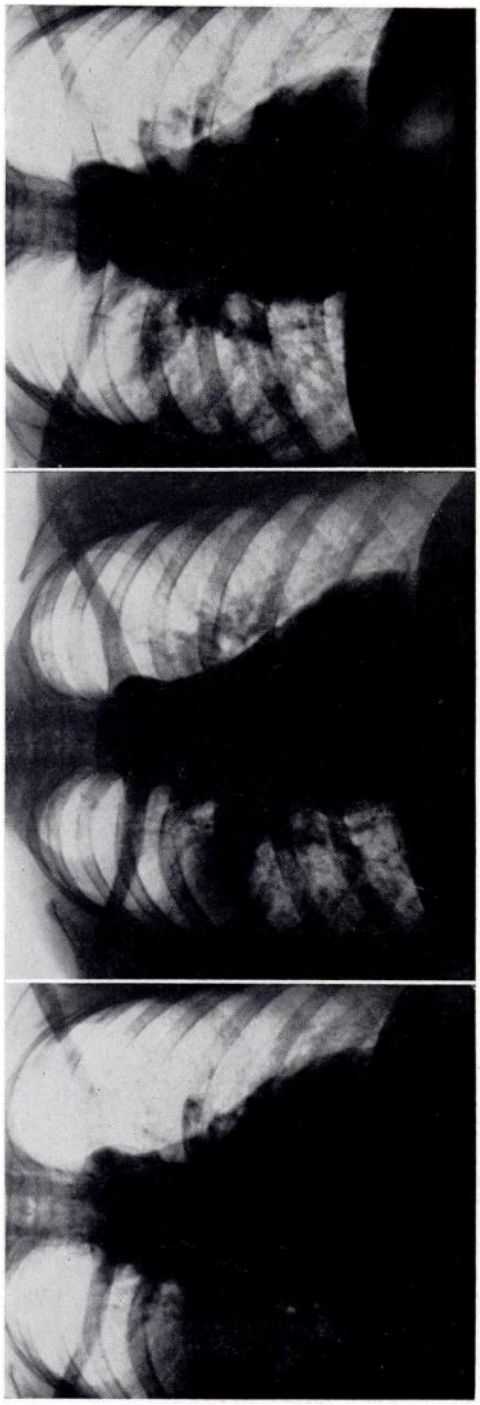

FIGURE 4 FIGURE 5 FIGURE 6

Fig. 4: A woman of 24 years. Acute onset of disease June 1944, ordinary sanatorium regime to November 1945 when she had an acute spread in the right lung with high fever, sputum positive (slide). X-ray November 13, 1945 before treatment: Diffuse infiltration of the right middle and lower part of the lung. PAS instituted November 15 in a dose of 14 grams PAS granules a day and continued to March 27, 1946.—*Fig. 5:* The same case on December 12, 1945. Afebrile. X-ray shows considerable clearing of the lung field, especially the lower part.—*Fig. 6:* The same on March 19, 1946. Continued clearing of the infiltrations in the middle part of the lung. Sputum still positive (guinea pig). In May she had a relapse on the right side with a cavity of walnut size. She responded favorably on retreatment with PAS and left the hospital February 4, 1949, sputum negative, and has since had no relapse.

Tracheo-bronchial Tuberculosis:

At several meetings of the Swedish Tuberculosis Association during the past years cases of tracheo-bronchial tuberculosis—including laryngitis—treated with PAS have been presented. Carstensen especially has stressed the striking effect of PAS in these cases and in all forms of tuberculosis in the mucous membranes. Vallentin has also reported more cases with a good effect. von Rosen has compared streptomycin with PAS treatment using aerosols and has seen good effect of streptomycin but no effect of PAS. The failing effect of PAS in aerosols could be anticipated as it is absorbed too quickly from the mucous membranes to produce any therapeutic effect even if given three times a day as inhalations during 15 minutes.

Intestinal Tuberculosis:

The most dramatic effects of PAS in the treatment of tuberculosis has been achieved in cases of intestinal tuberculosis as reported by Carstensen and Sjolin.[13] The material consisted of 22 cases of pulmonary tuberculosis complicated with intestinal localizations, verified by x-ray in 21 cases and postmortem in the 22nd. Twenty of the 22 cases had exudative cavernous pulmonary lesions, all with bacilli in sputum. In the other two cases the pulmonary process was predominantly of a nodose type and rather stationary. Most of the patients (20) had abdominal pains continuously, tenderness in the right iliac fossa and diarrhea, high temperature and sedimentation rate. All patients were seriously ill and the prognosis considered doubtfull or unfavorable—in some cases hopeless.

Before the PAS treatment the patients had been hospitalized for five to seven months and all forms of treatment tried without success.

The *treatment with PAS* was continued for three to 15 months and was often started over again in connection with performed operations. PAS was given in periods of three to six weeks with free intervals of about a week. The dosage varied from 6 to 14 grams PAS granules a day and was given by mouth in four to six doses. A dosage of 14 grams was generally used but in some cases not tolerated and the treatment therefore often commenced with a lower dose (6, 8 or 10 gms).

The *effect of the treatment* was in the most striking way evidenced by the improvement of the *intestinal symptoms*. All the patients were nearly or completely freed from their abdominal complaints within two to four weeks. The severe diarrhea, refractory against constipating drugs, ceased and so did the often unbearable pains. After-treatment barium enemas showed roent-

genographic improvement in five cases out of the examined 11 patients with total regression in two. In one case with fatal issue the necropsy proved that the intestinal process was in a healing phase.

The effect of PAS on the *general condition, temperature, sedimentation rate* and *weight* was in several cases even more pronounced than in cases of pulmonary tuberculosis. In 15 the weight increased 1 to 23 kg., simultaneously with the general well-being. In seven cases it remained unchanged or decreased. The temperature became normal in 15 out of the 19 patients who were afebrile, while the other four showed only initial or incomplete fall of the temperature. In 11 cases the sedimentation rate became normal. In cases, where the temperature and sedimentation rate remained high, far advanced and progressive lesions of the lungs were present. There was a rather rapid increase in the hemoglobin, when low before treatment.

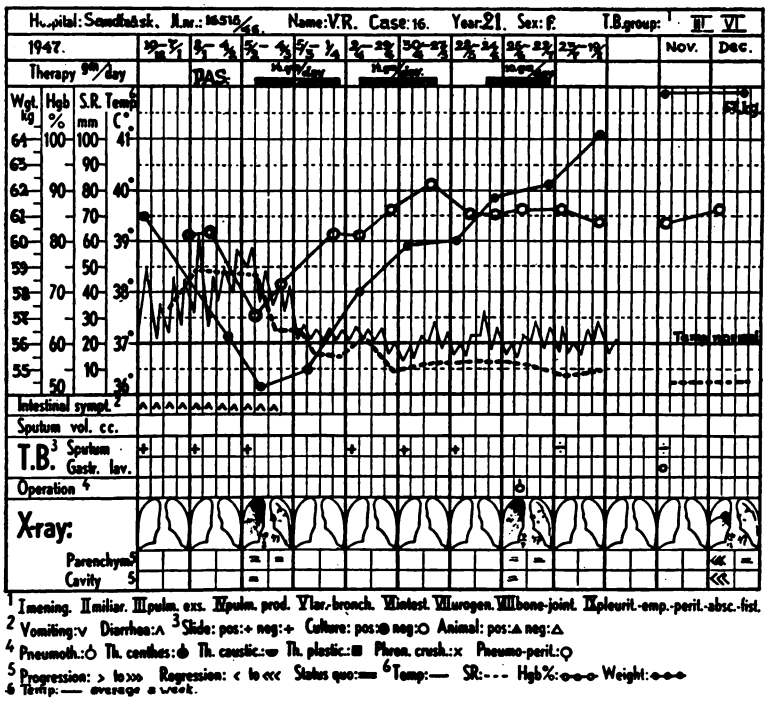

FIGURE 7: Case of pulmonary tuberculosis complicated with intestinal tuberculosis. Observe the high fever during nine weeks before treatment accompanied with a sharp drop in body weight and hemoglobin. After the institution of PAS the fever decreased and is nearly normal after three weeks and the sedimentation rate follows the drop in temperature down to normal values. The diarrheas disappear after two to three weeks treatment and the body weight and hemoglobin respond with a dramatic increase. After *Carstensen and Sjolin.*

As to the *pulmonary lesions* there was observed roentgenographic regressions in eight cases having fresh exudative processes. In two it was possible to institute pneumothorax and five have undergone successful thoracoplasties.

Of the 22 cases treated, 19 improved, three became worse, and one of them died.

In order to visualize the changes during treatment one of Carstensens and Sjolins cases should be mentioned—a female, born 1926.

Pulmonary tuberculosis was diagnosed in November 1944: exudative cloudy lesions in the left middle lobe and fibrotic, nodose processes all over the right upper lobe. Thereafter the patient was treated at several sanatoria and admitted to Sandtrask in July 1945. Left pneumothorax was instituted in December 1945. Thereafter the lung lesion remained on the whole unchanged until November 1946, when some progress with a small cavity in the right apex was observed. Since November 1946 also abdominal symptoms with pains, diarrhoea, tenderness in the cecal region, high, remittent temperature (the patient was previously afebrile), loss of weight, high sedimentation rate. *Barium enema in February 1947:* Pronounced changes in the cecal region. *PAS treatment was started on February 10, 1947.* There was immediate improvement and the abdominal symptoms completely stopped after 10 to 14 days, the general condition quickly improved (Fig. 7). The lung lesion remained on the whole unchanged with the small right apical cavity and bacilli in the sputum. Right pneumothorax was instituted on July 9 with good results. After pneumothorax the sputum converted to negative. *Barium enema on October 3, 1947* showed marked regression. The patient was discharged from the sanatorium in January 1948. She was in an excellent condition, had no symptom and was able to start work.

Another similar investigation on about 20 cases of intestinal tuberculosis was presented at the Nordiske Tuberkulose lagekongress in Helsingfors, 1949 by Kallquist.[14] The results were in full agreement with the above mentioned.

Encephalo-meningeal Tuberculosis:

The experience in the treatment of these forms of tuberculosis with PAS is rather limited because of their low frequency in Sweden. The writer has treated six cases, none of them living after one year. There is generally seen initial improvement and the patients have been kept alive for weeks or months. In a few cases death suddenly occurred during improvement, assumingly due to hydrocephalus internus, the presence of which was verified by necropsy. Microscopic examination showed that the processes in the brain and the meningeas were in a healing phase with fibrotic envolvement of the aqueductus leading to the hydrocephalus.

PAS was in the first cases given as a permanent intravenous 2 per cent infusion with a total dose of 20 to 30 gm. PAS in 24 hours. However, thrombophlebitis occurred regularly after three

to five days. In other cases peroral administration of the sodium salt-enteric coated in small granules—was used in the same dosage. Intestinal complaint (diarrhea) developed after using 30 grams per 24 hours. In two cases a 2 per cent PAS solution was given by duodenal tube instead of intravenously and high blood concentrations (20 to 25 mg. per cent) were found with values of 10 to 12 mg. per cent in the cerebrospinal fluid. Usually the concentration in the cerebrospinal fluid is one-third to one-fourth of the blood concentration. Therefore the unsatisfactory results in the treatment of encephalo-meningeal tuberculosis is not due to unsatisfactory penetration of the cerebrospinal barrier but rather to a low solubility of PAS in the brain tissue. Treatment of this disease with PAS alone can thus not be recommended. Combined therapy with shorter periods of streptomycin treatment together with permanent PAS therapy has been successful (Carstensen and Soderhjelm[15]).

Miliary Tuberculosis:

Miliary tuberculosis has reacted better on PAS treatment than encephalo-meningitis. In the mentioned team work on pulmonary tuberculosis four cases of miliary tuberculosis (from Renstroms Hospital) were included. In the Childrens Hospital in Gothenburg a few cases have been successfully treated (Y. Akerrhén and the writer) without relapses after one to one and one-half years. A detailed description of these cases has not yet been published. Combined therapy with streptomycin has been more successful than PAS or streptomycin alone (Carstensen and Soderhjelm).

Tuberculosis of the Kidney and Urinary Tract:

About 60 cases of urogenital tuberculosis have been treated by E. Ljunggren and O. Obrant at Sahlgrens Hospital in Gothenburg and at the Ravlanda sanatorium, connected to the hospital as a specialized ward for these cases and in charge of Dr. Ljunggren. Preliminary reports on kidney tuberculosis (Ljunggren[16]) have been presented, from which the following data are collected. In many of the cases combined chemotherapy with PAS, calciferol, streptomycin, chaumogra oil or TB I has been used. As these cases are unsuitable for elucidating the therapeutic effect of PAS they are not mentioned here. In other cases the treatment could not be continued for a sufficient length of time due to social or economical factors. Therefore, only cases being under the treatment, ward and observation for more than one year will be mentioned.

None of the cases had active pulmonary tuberculosis. The examination of the patients included analysis of the urine for tubercle bacilli (culture and guinea pig tests) once a month and in men

even examination of seminal fluid or prostate secretion if negative in the urine, non-protein nitrogen, urine cast and urea clearance. Intravenous pyelogram and, if not considered dangerous, cystoscopy was undertaken. The patients were afebrile and had normal or slightly elevated sedimentation rate. Three cases of *bilateral* kidney tuberculosis should be mentioned.

The first was a woman, aged 32, with painful cystitis and several small ulcers in the bladder. The pyelogram showed bilateral changes in the upper and lower calyces. She was treated with PAS in a dose of 8 to 10 grams PAS granules a day for 14 months altogether with a few free intervals of one to two months. The pains from the cystitis improved rather soon during the treatment and after three to four months they had disappeared together with the ulcers in the bladder. After seven months there was conversion in the urine and the guinea pig test has been negative for 18 months (more than 10 examinations). The processes in the calyces have shown signs of healing—partly with calcification—on the x-ray films.

The second case was a woman of 48 years. The pyelogram showed processes in both kidneys but there was no cystitis. She was treated for 14 months without interruption with eight grams PAS granules a day (equal to 6 grams PAS). The guinea pig test was positive once during the first week of treatment. Seven consecutive tests during the following year were negative.

The third case was a man of 35 years, with complicating genital tuberculosis. In one kidney two small calcifications were seen. The urine from this kidney was positive in guinea pig innoculation. The other kidney showed an abnormal pyelogram. After eight months treatment with eight grams PAS granules a day he converted in the urine and has since been negative (14 months with eight guinea pig tests).

Two cases of *unilateral* tuberculosis have been under observation for more than one year. Both of them had kidney and genitary tuberculosis. One of the cases was not operated upon because of chronic nephritis with improper kidney function test. He was treated for six months with PAS in a dose of eight grams granules increasing to 12 grams a day without conversion in the urine. Combined therapy with chaumogra oil and streptomycin resulted in conversion within a month. The role played by PAS in this case is not easy to evaluate. Possibly the patient had converted with PAS alone as more cases did so after seven to eight months treatment.

The other case was not operated upon because the kidney process was of a type where chemotherapy alone was considered prosperous. This suggestion was verified by conversion in the urine after two months treatment with 8 to 10 grams PAS granules a day and more negative tests during six months.

Of five cases with tuberculosis in the *remaining kidney after*

nephrectomy one case had positive guinea pig test after 11 months treatment with 10 grams PAS granules a day, a hopeless case with only a minor part of the kidney intact and complicated with genital tuberculosis. His cystitis improved however and he was freed from symptoms after two to three months treatment. Another case did not convert after seven months on 8 to 12 grams PAS granules, but he is nearly free from cystitis. A third case with a minor cavity in the kidney and genitary tuberculosis converted after eight months on 8 to 10 grams PAS granules and symptoms of cystitis disappeared after two months treatment. He has remained negative for five months. The remaining two cases have been treated too short a time to be mentioned here.

Recently Linden,[17] at the annual meeting of the Swedish Surgical Association in 1948, demonstrated a case of primary renal tuberculosis which had been treated with PAS for six months prior to the nephrectomy and in which the tuberculous process was in a healing stage. Linden, therefore, considered that it would have been better in this case if nephrectomy had not been carried out. Odelberg,[18] on the same occasion, reported a case in which cystitis, pyuria and tubercle bacilli in the urine occurred six months after nephrectomy for renal tuberculosis. A tuberculous lesion was seen in the kidney (destruction of the upper calyx) and a large tuberculous ulcer of the bladder was also found. After two and one-half months treatment with PAS the patient became free from symptoms, the pyuria had disappeared and the ulcer in the bladder had healed, the change in the calyx however, remained.

Summing up the results it can be said that PAS in nearly all cases has given amelioration of the cystitis and rendered the majority free from symptoms. Ulcers in the bladder have healed. Conversion in the urine has been seen in more cases within eight months treatment and remained negative (6 to 12 months observation time). No case has shown progression on the x-ray during the treatment. A higher dosage of PAS than here used may give better results.

Skin Tuberculosis:

Lemming[10] in 1948, reported a case of chronic skin tuberculosis (history 10 years) in which healing of a hand flat sized ulcer on one foot occurred after six weeks local treatment with a 10 per cent PAS solution. This was applied with a gauze wetted in the solution and changed several times a day. There was a relapse soon after the healing but retreatment healed the ulcer again and it has remained so after-observation for more than one year.

Carstensen recently presented three cases of lupus vulgaris also treated locally with PAS with good result. One of them was treated

with Finsen light and vitamin D without success. The ulcerations around her nose prohibited her from living among other people. The disease healed on PAS within six months.

Other Forms of Tuberculosis:

Little experience has been reported on the effect of PAS on other forms of tuberculosis as othopedic and sinus tuberculosis and lymphadenitis. Orthopedic cases seem to react slowly or not at all on peroral treatment, possibly better if local treatment can be applied. Two cases of otitis have healed on peroral PAS (Smars and Kempe[19]). Cases of tuberculous peritonitis and salpingitis have also responded favorable on peoral PAS treatment.

Surgical Prophylaxis:

From a theoretical point of view PAS should be well adapted for protection in operations as resistance to PAS is not generally developed during treatment and coming late if at all. The few reports on its use pre and postoperatively are encouraging. Odelberg[20] and Bruce and co workers[21] have this year presented papers on the subject which will soon be published.

Combined Chemotherapy:

In the above presentation the use of PAS combined with other chemotherapeutics has not been mentioned. The reason for this is that representative and conclusive series have not yet been published. However, PAS combined with sulfa drugs or penicillin was early used by Vallentin in the local treatment of empyema with mixed infections and especially by Westergren and co workers[22] in pulmonary tuberculosis (peroral or parenteral). Westergren has stressed the beneficial effect of changing from one drug to another, using PAS, streptomycin, penicillin and different sulfa drugs or a few of them together. He also observed a delayed or diminished emergence of resistance to streptomycin when PAS was simultaneously given. Carstensen and co workers have, as mentioned above, used PAS continuously with shorter periods of streptomycin in miliary and encephalo-meningeal tuberculosis. Recently Kristensson[23] presented a series of far advanced and hopeless cases of pulmonary tuberculosis with multiple cavities. With combined PAS, streptomycin and penicillin given continuously all together a dramatic effect was achieved in the majority of the cases.

Ambulatory Treatment:

The absence of real toxic side effects of PAS and the peroral use invites to the ambulatory use of the drug under controlled conditions. In Stockholm Bluhm[24] has started the ambulatory

treatment in a small series from his dispensary station and presented preliminary results. In Gothenburg a similar study is going on.

When reviewing the work on PAS during the five years it has been available to use in the clinic, it must be emphasized, that the experience in many respects is rather restricted. This is partly due to the limited supplies available during the first two years and partly to the high price. Difficulties in overcoming the intestinal complaints connected to the acid character of PAS has been a third limiting factor. As the new synthesis of PAS from meta-amino-phenol simplifies the production, the supplies should be sufficient and the price acceptable. Whether PAS should be used routinely as an acid-enteric coated, or as the sodium salt, is still a question to be answered.

The optimal dose of PAS for the different forms of tuberculosis has not been satisfactory elucidated. That the highest doses (20 to 30 grams Na-PAS) should be used in cases of miliary and encephalo-meningeal tuberculosis seems justified and that lower doses than 11 to 12 grams PAS (14 grams granules) a day can be used in kidney-urinary tuberculosis due to the high concentrations in the urine. For most of the other forms of tuberculosis a dose of 10 to 12 grams PAS giving blood concentrations of two to six mg. per cent seems reasonable.

That PAS should be given *continuously,* if possible, has been illustrated by the increase in sedimentation rate and sometimes even in temperature when it has been stopped for a week or two. The length of the treatment should be determined for each case but it should be kept in mind, that even if amelioration in the general condition, the decrease in temperature and sedimentation rate are appearing early, the regressions of the lesions, at least in the lungs, are slower and the most demonstrable changes occurring between the third and sixth month. The treatment should naturally be continued as long as improvement is seen and usually the end state should be stabilized by another months treatment.

Recent investigations in vitro, in animal experiments and in the clinic seems to indicate that the combined therapy with PAS and streptomycin will give results superior to those with each drug alone. Beside that, the combined therapy has another perhaps still more remarkable feature, the depression or delay of the emergence of resistance to the drugs. This does mean that the duration of the treatment can be prolonged and perhaps widen the indication for their use.

REFERENCES

1 Lehmann, J.: The Lancet, 251:15, 1946.
2 Lehmann, J.: Svenska Lakartidningen, 43:2029, 1946.
3 Lehmann, J.: Revue Générale des Sciences, 54:222, 1947.
4 Vallentin, G.: Svenska Lakartidningen, 43:2047, 1946 and Nordisk Medicin, 33:147, 1947.
5 Vallentin, Tornell, Beskow, Carstensen, Thune, Helleberg and Lehmann, J.: Transactions of the XIV Nordiske Tuberkuloselagekongres in Copenhagen, 1948 (in press). The main part of the paper is also printed in "Le Poumon," No. 2 and 3 (March-June), p. 193, 1949.
6 Rosdhal, K. G.: Svensk Kemisk Tidskrift, 60:12, 1948 (in english).
7 Alin, K. and Helander, S.: Acta Tuberc. Scand., 22:283, 1948.
8 Alin, K. and Difs, H.: Nordisk Medicin, 33:151, 1947.
9 Dempsey, T. G. and Logg, M. H.: The Lancet, 253:871, 1947.
10 Lemming, R.: The Lancet, 256:200, 1949.
11 Lehmann, J.: Transactions of the XIV Nordiske Tuberkuloselagekongres in Copenhagen, 1948 (in press).
12 Bachman, S., Birath, G., Bruce, T., Karth, B., Lemming, R., Lindgren, G. and Lundquist, J.: Transactions of the XV Nordiske Tuberkuloselagekongres in Helsingfors, 1949 (in press).
13 Carstensen, B. and Sjolin, S.: Svenska Lakartidningen, 45:729, 1948 and "Le Poumon," No. 2 and 3 (March-June), p. 209, 1949.
14 Kallquist, I.: Transactions of the XV Nordiska Tuberkuloslakarkongress in Helsingfors, 1949 (in press).
15 Carstensen, B. and Soderhjelm, L.: Nordisk Medicin., 40:2039, 1948.
16 Ljunggren, E.: Journal D'Urologie, 1949 (in press).
17 Linden: Transaction of the Swedish Surgical Association, 1948.
18 Odelberg, A.: Ebenda.
19 Smars, G. and Kempe, S. G.: Nordisk Medicin. (in press).
20 Odelberg, A.: Paper presented at The Second Commonwealth and Empire Health and Tuberculosis Conference in London, 1949 (in press).
21 Bruce, C., Birath, G., Crafoord, C. and Uggla, L. G.: Transactions of the XV Nordiska Tuberkuloslakarkongress in Helsingfors in 1949 (in press).
22 Westergren, A.: Nordisk Medicin., 33:155, 1947.
23 Kristensson, A.: Svenska Lakartidningen, 46:1317, 1949.
24 Bluhm, I.: Transactions of the XV Nordiska Tuberkuloslakarkongress, Helsingford, 1949 (in press).

The Treatment of Tuberculosis in Sweden with Para-Aminosalicylic Acid (PAS): A Review

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