The problem of chemotherapy of patients with destructive pulmonary tuberculosis, previously ineffectively treated and having the resistant strains of mycobacterium tuberculosis (MTB) is a very complex and remains in the focus of phthisiatricians. In recent years, due to the increase of multi- and poli-drug resistance of MTB (MDR-TB, PDR-TB) phthisiatricians' attention is paid again to PAS (Para-Aminosalicylate Sodium) - one of the first TB drugs widely used in 40-70s of the last century [1, 2, 3, 4]. This drug was used for patients with various forms of tuberculosis, especially with newly diagnosed destructive tuberculosis of the lungs, usually in combination with streptomycin and isoniazid. Moderate anti-TB and anti-inflammatory action of PAS, its ability to slow the development of MTB resistance to drugs used in combination with PAS, synergistic effects when using with isoniazid and streptomycin were detected [3, 2, 4, 1].

Then for decades PAS was almost not used in chemotherapy of tuberculosis, as more effective basic drugs were used in that time (rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide) as well as some second-line drugs. Only in recent years due to the growth of multi-drug-resistant tuberculosis and difficulties in its treatment physicians again drew attention to PAS and began to use it - this time for MDR-TB along with a second line drugs. But still there are virtually no works about the effectiveness and therapeutic opportunities of PAS use for this patients, and in general in patients with previously treated ineffectively, mainly chronic destructive pulmonary tuberculosis. Only one work of recent years [5] contains data regarding ways to prevent or reduce allergic reactions to PAS.

Therefore, it's appropriate to study the results of PAS use as a part of complex chemotherapy for previously ineffectively treated patients with destructive resistant TB of the lungs (especially chronic); determine the therapeutic and side effects, and optimal methods of PAS use, the place of this drug in the treatment of this contingent of patients.

All these issues were the subject of our research. At present the treatment with PAS was performed in the department of tuberculosis of Institute of Tuberculosis and Pulmonology in 70 patients with destructive pulmonary tuberculosis. In 39 of them (55.7%) there was a chronic destructive process with duration of from 2 to 20 years, treated earlier for a long time or ineffectively, with MDR-MBT (4 outpatient category). In 16 persons (22.9%) with tuberculosis duration from 6 to 24 months destructive process was previously treated ineffectively, it was often accompanied by a multi- or poliresistance of MBT (2nd category). In 6 patients (8.6%) recurrence of destructive tuberculosis was detected (also 2nd category).

In 39 of them (55.7%) there was a chronic destructive pulmonary tuberculosis. In 53 (77.9%) persons a large amount of MTB in smears was detected. According to bacteriological studies made in the Institute (as well as in dispensaries) MTB resistance to 1 anti-tuberculosis drug was found in 3 persons (4.4%); to 2 drugs - in 5 (7.3%) patients, to 3 drugs - in 7 patients (10.3%); to 4 - in 15 patients (22.1%), to 5-6 - in 20 patients (29.4%) and to 7-9 drugs - in 8 patients (11.8%). Total it was 58 patients (85.3%) with the resistant strains of MTB. Only in 10 persons (14.7%) isolated strains remained sensitive to all drugs. Resistance to isoniazid had been confirmed in 53 patients (77.9%), to rifampicin - in 51 (75.0%), to streptomycin - in 52 (76.5%), to ethambutol in 18 (26.6%), to ethionamide - in 35 (51.5%), to kanamycin - in 26 (38.2%); to other drugs (fluoroquinolones, amikacin, clarithromycin, etc.) - much less often (in 17.7% of cases), and to PAS it was not detected at all. Overall multi-drug resistance occurred in 45 patients (66.2%), poli-drug resistance - in 10 (14.7%) and mono-resistance - only in 3 patients (4.4%).

PAS was used intravenously as well as by oral route. For intravenous administration "Paskonat" produced by company "Yuria-pharm", Ukraine, was used in our study. This is a solution of para-aminosalicylate sodium for infusion of 400 and 200 ml bottles. 400 ml of solution contain 12 g of para-aminosalicylate sodium. The solution was administered intravenously with a rate of 40-60 drops per minute. PAS daily dose of 400 ml (occasionally 300-350 ml) was administered for 1.5-2 hours. The drug was administered on daily and intermittent (every other day or 3 times a week) bases.

For oral administration PAS in the form of enteric pellets produced by "BBC Pharmaceuticals and Chemicals Ltd", India, was used. Daily dose of PAS per os as well as for intravenous infusion usually was 12 g, 8-12 g for some patients (150-200 mg per 1 kg body weight). Patients took PAS in 0.5-2.5 hours after eating, with mineral water or milk, 1-2 times a day, daily or intermittently (every other day).

In general, PAS was used only intravenously in 35 patients, only per os - in 12 and by both ways - in 23 (as a rule intravenously at a start and then per os, rarely - vice versa or simultaneously: on some days - intravenously, on other days...
- per os). Daily dose of PAS was 12 g in 61 patients and 8-10 g - in 9 patients. PAS was used only on a daily basis in 29 patients, only intermittently - in 34 and by both methods (from the beginning of treatment daily, then - intermittently) - in 7 patients.

PAS was administered in a combination with 3-5 or more anti-TB drugs to which sensitivity of MBT were detected and (or) that were not previously used or used for a short period of time. Most often these drugs were fluoroquinolones, clarithromycin, amikacin, kanamycin, ethambutol, ethionamide (prothionamide), sometimes pyrazinamide, rifabutin, doxycycline and amoxiclav, very rare - isoniazid and rifampicin. These drugs were administered in usual dosage daily or intermittently (every other day, 2-3 times per week). PAS was used in 15 patients for 2-3 months, in 20 - for 3.5-5 months, in 19 - for 5-6 months and in 16 - for 7-12 months.

Combination chemotherapy with the inclusion of PAS resulted after the first stage of treatment in improvement of the clinical condition of patients and reduction of subjective symptoms. Thus, in the first 3-4 weeks and next months of chemotherapy temperature was decreased or normalized, other symptoms of intoxication decreased as well as sputum and cough intensity. Sputum gradually lost its purulent character. Complete disappearance of these symptoms was observed in 38 patients (54.3%) and reduction - in 24 (34.3%). Erythrocyte sedimentation rate (ESR) was normalized by 2-6 months in 33 (52.4%) of 63 patients with accelerated response to treatment and markedly decreased in 20 (31.7%) patients. Leukocytosis, left shift and lymphopenia disappeared in 86-75% of cases, mainly in the first 4.1 months.

After 1 month of treatment amount of MBT detected in the sputum was reduced markedly both in sputum smear and culture. In subsequent periods of treatment MBT was rarely identified by both methods or was not found at all.

After 1 month of complex chemotherapy with inclusion of PAS MBT was not detected in 4 (5.9%) out of 68 previously MBT-positive patients, after 2 months - in 12 (17.7%), after 3 months - in 9 (13.2%), after 4 months - in 5 (7.4%), in 5-6 months - in 6 (8.8%) and after 7-8 months - in 3 (4.4%) patients. MBT was not detected in 39 patients (57.4%) in (3.31 ± 0.25) months in average. In 17 people (25.0%) decrease of MBT amount was observed, and in 12 (17.6%) there was no significant changes. Bacteriological results should be assessed as significant, taking into account the severity of contingent of patients.

Complete or significant resorption of infiltrative, cheesy and node formations in the lungs (usually in 3-7 months) was achieved in 40 patients (57.1%), partial - in 21 (30.0%), no significant changes - in 7 (10.0%) and worsening of changes - in 2 (2.9%) patients.

Reducing the size of cavities, resorption of the surrounding infiltration and thinning of the walls of cavities was started after 1-2 month of using of PAS and other drugs and reached its maximum (up to the healing of cavities) typically to 3-7 months. Then, often took place at a slower pace further regression of remained cavities. In some patients the same positive changes of cavities has not occurred. After 2 months of chemotherapy cavity were healed in 3 persons (4.3%), after 3 months - in 4 (5.7%), after 4 months - in 5 (7.1%), after 5 months - in 4 (5.7%), after 6 months - in 5 (7.1%) and in 7-9 months - in 5 (7.1%) patients. In general, cavities healing was achieved in 26 out of 70 patients (37.1%) and average time of healing was 4.88/-0.36 months. During cavities healing various residual changes were formed - fibrous bands, indurations, cirrhosis, dense foci, cystic formation, etc.

In 31 (44.3%) patients only partial, but often quite significant regression of cavities were achieved - downsizing, thinning of the walls and the healing of the cavities, accompanied by a noticeable resorption of infiltrative changes, in 14 patients sputum culture has become negative. Thus, complete or partial regression of cavities has been achieved in the majority of patients - 57 (81.4%). Only in 13 (18.6%) patients with the most severe polycavernous process and large cavities positive dynamics was not observed: in 11 (15.7%) the size and number of cavities were not changed, and in 2 (2.9%) even increased.

In general, direct results of complex chemotherapy with inclusion of PAS were following: in 26 patients (37.1%) - a significant improvement (healing of cavities, negative culture and elimination of other manifestations of active TB), in 15 (21.4%) - improvement (decrease of MTB amount or negative culture/smear, partial regression of cavities, the elimination or significant reduction of other manifestations of the process), in 19 (27.2%) - partial improvement (mainly symptomatic and partial resorption of infiltrative formations, often some regression of cavities and reducing of MTB amount), and in 10 (14.3%) patients with severe chronic polycavernous process and multi-drug resistance to 5-9 drugs course of the disease has not improved: in 8 of them (11.4%) it has not significantly changed, and in 2 (2.9%) it has deteriorated. Thus, in a most patients with very severe process - 41 (58.6%) - positive results were obtained after chemotherapy containing PAS.

We analyzed the dependence of outcomes on various factors, primarily the form of disease. Of the 39 patients with chronic destructive pulmonary tuberculosis, with process duration from 2 to 20 years (4 category) MBT disappeared in 19 (48.7%), and cavens healed in 9 (23.1%) persons; among 31 patients of 2d and 1st category (TB duration 6-24 mos) MTB wasn't detected after treatment in 20 (69.0%) out of 29 previously MBT-positive patients, cavens healed in 17 (54.8%); difference in frequency of healing of cavities was highly reliable (P <0.01), and difference in frequency of the disappearance of a MTB significant, but not statistically reliable (P> 0.05).

19 (44.2%) patients out of 43 patients with isolated resistant to 4-9 anti-TB drugs MBT were culture-negative after treatment, and cavities were eliminated in 9 (20.9%), meanwhile among 25 people with resistant to 1-3 drugs or sensitive MTB, they disappeared in 20 (80.0%) patients and cavities healed in 17 (63.0%) out of 27 (2 patients were MTB-negative before treatment); difference in frequency is highly reliable (P<0.01-0.001).

A comparison of the effectiveness of intravenous and oral methods of PAS administration was carried out. Since 23 patients used both ways of PAS administration (preferably
sequential), they were divided into groups depending on which method was used significantly longer. Thus, among 48 persons receiving PAS only or mainly intravenously (47 were MBT positive), 28 (59.6%) ones have become culture-negative, and caverns healed in 19 (39.6%) patients. Among 22 patients with only or predominantly oral use of PAS MBT were not detected after treatment in 11 out of 21 patients (52.4%) and cavities healed in 7 (31.8%) patients. Partial regression of cavities in intravenous and oral administration was observed respectively in 22 (45.8%) and 9 (40.9%) patients. Consequently, the effectiveness of these methods is very similar (P > 0.5). We can notice a small tendency to better results in intravenous use of PAS - perhaps due to the greater concentration of drug in blood.

In case of only or mostly everyday use of PAS MBT disappeared in 19 out of the 32 bacteria discharging (59.4%) patients, and caverns healed in 13 out of 33 people with cavities (39.4%). In only or predominantly intermittent PAS administration which was used in 37 patients (including 36 with the presence of MBT) MBT was not detected in 20 (55.6%), and caverns healed in 13 (35.1%) patients. These results are almost identical, with a little bit better results of a daily method (P > 0.5).

Comparison of chemotherapy results with and without inclusion of PAS is given in Table. In the control group of 72 patients with destructive, previously treated ineffectively, usually resistant TB of the lungs, which was identical to the experiment group (which used PAS) in the nature and duration of the process, drug resistance of MBT, previous treatment and age and sex characteristics, chemotherapy regimens of the same intensity and similar in composition but without PAS was used.

Data in table show much higher and faster results in case of chemotherapy regimens with PAS use. In the experimental group MBT wasn’t detected in 57.4% patients and in control one - only in 40.0% (P < 0.05) with medium duration of treatment until MBT negative respectively of (3.31 ± 0.25) months and (4.29 ± 0.34) months (P < 0.05).

In case of use of chemotherapy with PAS healing of cavities occurred in 37.1% patients, partial regression of cavities - in 44.3%, and in general regression of cavities (complete and incomplete) - in 81.4% of patients. Meanwhile in the control group, these changes occurred only in 29.2%, 36.1% and 65.3% of cases respectively, difference from the experimental group in the total regression of cavities were reliable (P < 0.05), and separately for healing of cavities and for their partial regression though noticeable but not yet reached a reliable level (P > 0.2).

It is important that when taking PAS caverns healing was much faster - on average (4.88 ± 0.36) months with PAS and to (6.05 ± 0.45) months without PAS (P < 0.05).

Thus, the use of PAS in patients with destructive, of resistant, mainly chronic pulmonary tuberculosis enhanced the frequency of MBT-negative state by 17.4%, cavities healing - by 7.9%, total regression of cavities - by 16.1% and accelerated the disappearance of MBT and cavities healing to 0.98–1.17 months. Increase due to PAS addition effectiveness of treatment we explain by the bacteriostatic activity of PAS against different strains of the MBT, including those resistant to anti-TB drugs of I and II line. In addition, PAS has the ability to potentiate the action of some drugs, especially isoniazid.

During the treatment with PAS character of MBT resistance to essential medicines and spice was not significantly changed, confirming data of 50-70th years of last century on a high ability of PAS to prevent development of resistance of MBT to drug in combination with which it is used [2, 3, 4]. Not less important was the fact that there was no cases of MBT resistance to PAS development during all observational period.

The main side effects of PAS were gastro-intestinal disorders: nausea, belching, heartburn, appetite loss, rarely vomiting, abdominal pain, flatulence, diarrhea. These effects occurred predominantly at 1st months of treatment, sometimes at 2-3d months and later, they were of different intensity and duration (from several days to 1-3 months). Total dyspeptic side effects were observed in 18 out of 70 patients (25.7%), including in intravenous PAS administration - in 12 (20.7%) of 58 persons who received the drug intravenously and in oral administration - in 11 (31.4%) out of 35; difference was noticeable, but has not reached the level of reliability (P > 0.2). Of the above number of patients in 5 GI disorders developed both in intravenous and oral administration of PAS (23 patients used both ways of administration).

Severe dyspeptic reaction in 9 patients (12.9%) led to the final withdrawal of PAS, then these effects quickly disappeared. Reason for PAS withdrawal in 3 subjects was intravenous method, in 3 - oral and 3 - both methods, ie GI intolerance in intravenous PAS administration has been confirmed in 6 out of 58 patients (10.3%), while in oral - in 6 out of 35 (17.1%), P > 0.2. Moderate or minor dyspeptic disorders were observed in total in 9 patients (12.9%). Gastrointestinal disorders were decreasing or disappearing at lower doses of PAS (from 12 g to 8-9 g), with short- term termination of taking it, when used daily dose of PAS divided

### Table. Effectiveness of chemotherapy in patients with destructive, previously treated ineffectively pulmonary tuberculosis with and without PAS

<table>
<thead>
<tr>
<th>Regimens of chemotherapy</th>
<th>Number of patients</th>
<th>Negative culture</th>
<th>Caverns regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>MBT positive</td>
<td>rate</td>
</tr>
<tr>
<td></td>
<td>abs.</td>
<td>%</td>
<td>abs.</td>
</tr>
<tr>
<td>With PAS</td>
<td>70</td>
<td>68</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without PAS</td>
<td>72</td>
<td>70</td>
<td>28</td>
</tr>
</tbody>
</table>

Note: * - significant difference between the main and control group (P < 0.05)
in 2 times, often with replacement of oral administration with intravenous (rarely opposite), and the application of intermittent (every other day) schedule.

GI side effects occurred in 12 (36.4%) out of 33 patients in which PAS was used only or mostly daily, and only in 6 (16.2%) out of 37 persons with only or mostly intermittent administration of PAS (P < 0.05 ), including severe GI disorders that were observed respectively in 6 (18.2%) and 3 (8.1%) patients (difference is significant, but has not reached the level of reliability: P > 0.2).

Changes in the gastrointestinal tract were less pronounced with three meals a day, correct regimen of PAS taking - in 0.5-2.5 hours after eating, in a different time with other anti-TB drugs, which also can have GI side effects. Very important is also slow (at least for 1.5-2 hours) intravenous administration of PAS, because in the case of the more rapid infusion severe gastrointestinal and general reactions are possible.

From the other side effects PAS caused in 4 patients (5.7%) allergic reactions - hives, flushing and itching, eosinophilia. They appeared in the first weeks of PAS use (in 2 patients in IV administration and in 2 patients in oral use) and decreased or disappeared when taking antihistamines, and in 1 person (1.4%) led to discontinuation of the drug.

In 2 patients (2.9%) hepatotoxic effects (along with dyspeptic) and in 1 (1.4%) - nephrotic effects were recorded during polychemotherapy. But these reactions occurred in case of PAS combination with drugs that may be hepatotoxic (pyrazinamide, ethionamide, isoniazid or rifampicin) or nephrotic (kanamycin or amikacin). Therefore it was difficult to find a role in PAS in these side effects.

In addition, in intravenous use in one patient (1.4%) there was a pronounced general reaction in the form of weakness and dizziness (as well as GI side effects) and in 2 (2.9%) - phlebitis at the site of infusion, which forced us to change the way of administration for the oral one.

In general, adverse events of various kinds of PAS were recorded in 23 (32.9%) of patients (dominated diarrheal disorders, and in 5 people were two syndromes of side effects), including pronounced reaction that led to the drug withdrawal - 10 (14.3%) patients. Intravenous PAS administration caused side effects in 16 (27.6%) out of 58 patients who used this method and oral - in 12 (34.3%) out of 35, including pronounced reaction - respectively in 7 (12.1 %) and 6 (17.1%) persons. Thus, the intravenous method in comparison with oral somewhat, though not significantly less (P > 0.5), caused side effects of PAS.

It is advisable not to use PAS in gastric ulcer and duodenal ulcer, gastritis, duodenitis, hepatitis, liver cirrhosis, severe kidney disease, hypothyroidism, cardiac decompensation.

Conclusions
1. The results of the PAS use in the complex chemotherapy in patients with destructive, previously treated ineffectively, resistant TB of the lungs are significant: negative culture in 57.4% of people, cavity healed in 37.1% and partially regressed - in 44.3%, which accordingly is by 17.4%, 7.9% and 8.2% respectively higher than in chemotherapy regimens without the use of PAS. Terms of disappearance of MBT and cavities were shortened by 1 month.

2. PAS relatively often causes side effects (were recorded in 32.9% of patients), mainly GI (in 25.7%); in 14.3% of persons severe reactions were observed that disappeared rapidly after drug withdrawal.

3. Intravenous administration of PAS (Paskonat) somewhat less often provoked dyspeptic effects (20.7% of cases) than oral one (in 31.4%). The effectiveness of both methods is very close, with a slight advantage of intravenous one. This method is most appropriate to apply in the first phase of intensive chemotherapy, and then it can be switched to oral administration.

4. To improve PAS tolerability it is necessary to follow the contraindications for its use, have appropriate three regular meals, slow (at least for 1.5-2 hours) intravenous administration of a drug, taking per os in 0.5-2.5 hours after eating and in different time with other medicines that also can cause GI side effects, switching to the intermittent mode of administration. Intermittent method reduces GI disorders at least 2 times and has almost the same effectiveness as everyday use.

5. PAS has a high ability to prevent development of resistance to the anti-TB drugs, which are combined with this drug. Besides, we observed no one case of resistance to PAS development.

6. PAS along with other reserve drugs may take an important place in chemotherapy of destructive, previously treated ineffectively, resistant TB of the lungs.

LITERATURE

RESULTS OF PAS APPLICATION IN COMPLEX CHEMOTHERAPY OF PATIENTS WITH DESTRUCTIVE, INEFFECTIVELY TREATED PREVIOUSLY, RESISTANT PULMONARY TUBERCULOSIS

I. B. Byalik, L. M. Tsygankova, V. V. Davidenko, I. V. Slouch.

Abstract
PAS’s efficacy and tolerability was studied in 70 patients with multiply and polyclinically destructive, previously ineffectively treated pulmonary tuberculosis. Application of PAS in combination with 3–5 and more antituberculosis drugs (mainly of II group) led to discontinuation of M. tuberculosis (MTB) excretion in 57.4% of patients, healing of caverns in 37.1 % and caverns partial regression in 44.3 % of patients, which was higher on 17.4 %, 7.9 % and 8.2 %, accordingly, vs. treatment without PAS. Terms of MTB and caverns disappearance shortened on one month. PAS side effects (mainly gastroenteric) were registered in 32.9 % of patients, and in 14.3 % of them they were meaningfully expressed.

Intravenous injections of PAS (Paskonat) were more preferable in the beginning phase of intensive chemotherapy, and then it can be switched to oral administration.