PHTHISIOLOGISTS OF YAKUTIA: SCIENTIFIC AND PRACTICAL POTENTIAL

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Phthisiologists working in the field of therapy for pulmonary tuberculosis and development of new treatment methods started their scientific and practical work in the 1950s. The first two stages of the work became history by now; the 2000s were the beginning of the third stage – the quest for contemporary methods to treat and overcome M.tuberculosis drug resistance. Thesis works and patents for inventions give eloquent illustration of the close interconnection between science and practice.

Keywords: tuberculosis, Yakutia, research work, methods of treatment for pulmonary tuberculosis, Russian Federation patents.

Yakutsk Branch of the Tuberculosis Institute, AMS USSR, was opened in 1950 and its Therapeutics Department opened in the same year.

Sanatorium/resort treatment, sanitation and dietary treatment were the ways to treat tuberculosis in the XIXth century throughout the world. The wide use of pneumothorax started at the turn of the XXth century. Starting in the mid 1930s, surgical methods began to be used for treatment of tuberculosis. Discovery of streptomycin, the first anti-tuberculosis drug, was the first big step in development of etiotropic therapy. Intensive use of para-aminosalicylic acid (PAS), tibon, and isonicotinic acid hydrazide (INH) for treatment of tuberculosis began in 1954, while the use of new highly effective agents such as rifampicin, ethambutol, pyrazinamid started in the 1970s. The spectrum of anti-tuberculosis drugs has widened (fluroquinolons) since the end of the XXth century. One can see how all these periods in the history of anti-tuberculosis therapy are reflected in the history of pulmonary tuberculosis therapy in Yakutia.

Scientific activity of Yakutsk phthisiologists can be divided to 2 historical periods for convenience.

1st period (1950-1969): therapy of pulmonary tuberculosis in Yakutia was conducted under the leadership of the doctors from central Russian cities and institutes, who were invited to Yakutia by E.N. Andreev, the first Director of the Yakutsk Branch of Tuberculosis Institute, AMS USSR. Scientific explorations of that time, carried out by the Therapeutics Department of the Yakutsk Branch of Tuberculosis Institute (later Yakutsk Research Institute for Tuberculosis of the RSFSR

Ministry of Health) sought to introduce new etiotropic medications, and to develop better treatment regimens. Doctors sent to work in Yakutia studied the situation with tuberculosis in the republic, defended their theses based on study findings, and eagerly shared their experience and knowledge with Yakutsk phthisiologists, many of whom later underwent postgraduate education in central Tuberculosis Institutes and successfully defended theses.

2nd period (1970-2000): the followers of the invited Russian doctors, who proceeded to degrees and acquired practical experience, began to educate young doctors in Yakutia. This time was the period of search for new methods to treat destructive tuberculosis and endobronchitis, including the cases complicated with drug resistance of the causative agent. Based on the results of these studies, a number of theses were again defended, and some treatment methods were patented.

1st period. In 1950 F.D. Zaveleva (Cand.Med.Sc.) became the Head of the Therapeutics Department. She was the first to propose combination chemotherapy regimen that included tibon and small doses of streptomycin; this regimen proved highly effective in patients with early forms of pulmonary tuberculosis (1951). Intermittent therapy method was also developed and adopted at this period (S.I. Torgovkina).

Treatment method for pulmonary tuberculosis based on the use of antibacterial agents in combination with tuberculin (in various dilutions) was developed and eventually adopted to the practice of Therapeutics Department under the guidance of S.L. Pekarskaya, Cand.Med.Sc. (1955-1965); she also wrote a thesis on epidemiology and treatment of disseminated pulmonary tuberculosis in YASSR. The use of this method increased treatment effectiveness up to 55-60%. On E.N. Andreev's initiative, therapists started to use some biostimulators in combination chemotherapy for pulmonary tuberculosis.

S.S. Gavriliev and E.A. Ivanov, who came to work in the field of phthisiology following their fresh graduation from the Medical Institute, acquired their first experience in anti-tuberculosis work under the supervision of the doctors from Moscow. In 1965 S.S. Gavriliev, the resident physician in the Therapeutics Department defended his Candidate thesis entitled "Experience with the use of pasomycin for pulmonary tuberculosis" during postgraduate training in the Central Research Institute for Tuberculosis, AMS USSR. In 1968 E.A. Ivanov defended his thesis on "Desensitizing therapy in patients with pulmonary tuberculosis". In the following years, both of them had headed at different time the Therapeutics Department of the Yakutsk Research Institute for Tuberculosis.

2nd period. This period was the productive prime of Yakutsk phthisiologists – the trainees of Russian phthisiologic school and their successors in Yakutsk Research Institute for Tuberculosis.

In 1969 S.S. Gavriliev (Cand.Med.Sc.) became the Head of Therapeutics Department. He

supervised the development and practical adoption (first in the practice of Therapeutics Department and then over the republic) of the methods: single administration of daily doses of medications (N.I. Strod); express intravenous administration of isoniazid (E.A. Ivanov); methods for rectal administration of anti-tuberculosis agents and methods for administration of various nosotropic agents (beginning in 1972). Methods that were aimed at improving the clinical effectiveness of treatment allowed achievement of conversion of bacillary positive state in 80% of cases, cavity closure in 70-75%, and abrupt reduction of side effects in new cases of destructive pulmonary tuberculosis.

One of the particularly interesting methods developed by S.S. Gavriliev is the method for rectal drip administration of tubazide and PAS used in combination therapy of pulmonary tuberculosis in the extreme northern environment (Rationalization proposal certificate (local novelty) granted to Yakutsk Research Institute for Tuberculosis of the RSFSR Ministry of Health, issued May 13, 1977) [1]. The method proposed was novel, promising, and best suited for use in patients with concurrent gastric or renal disease. After 13 years of reviewal by The Pharmacological Committee of the Ministry of Health of USSR (Protocol No.14, issued August 26, 1988), this treatment method was approved for use over the country, and isoniazid and PAS were approved for rectal administration.

As the scientific staff of the Therapeutics Department participated in all-union scientific research program “Side effects of anti-tuberculosis medications, detected in health institutions, in various geographic areas of the Soviet Union”, study of side effects and intolerability of medications and development of prevention methods were under way. Serious attention was paid to developing alternative chemotherapy methods based on distinctive patterns of pathogenesis, extensiveness, localization and clinical form; such methods were needed for correction of therapy depending on the pattern of tubercular inflammation, and also for differential approach to treatment using antioxidants (Val’ N.S., 1995).

Studies on nosotropic treatment methods for tuberculosis initiated by S.S. Gavriliev have been continued by the studies of Lineva Z.E., resulting in successful defense of her Candidate thesis “Etiologic treatment for destructive pulmonary tuberculosis in the environment of extreme north” (1985) on the use of ultrasound in combination with methyluracil and insulin for treatment of pulmonary tuberculosis. Use of the method led to 2-3-fold reduction in frequency of side effects and faster conversion of bacillary-positive state and faster cavity closure (up to 90.0% of cases). Use of semiconductor laser in combination with medications for correction of oxidative/antioxidative disorders became another highly effective method to treat pulmonary tuberculosis (Vinokurova M.K., 1996, 2005). Use of EHF therapy (extremely high frequency therapy) in combination with

antioxidants likewise showed high treatment effectiveness (Yakovleva L.P., 1999).

Z.E. Lineva's Doctor thesis "Gastric dysbacteriosis and methods of its corrections in patients with pulmonary tuberculosis" (1995) was devoted to the study of the pathogenesis of gastric dysbiosis during currently used chemotherapy for pulmonary tuberculosis and development of novel ways to correct this dysbiotic state.

S.S. Gavriliev also guided the development of the following new treatment methods for destructive pulmonary tuberculosis: endobronchial administration of solibilized rifampicin [2]; deep phonophoresis of intercostally intramuscularly administered isoniazid [3]; inhalation of anti-tuberculosis agents diluted in silver water [4]; inhalation of kanamycin diluted in ammonia solution of silver nitrate, for pyogenic endobronchitis in patients, who have destructive pulmonary tuberculosis with polyresistant *M.tuberculosis* and non-specific flora [5]; intercostal administration of isoniazid in combination with laser exposure, for treatment of pulmonary tuberculosis patients with massive bacillary counts, and multiple destructions concurrent with endobronchitis (using deep photophoresis of intercostally administered 10% solution of isoniazid in combination with herbal therapy using 'breast tea') [6]. Alternative methods of medication administration allowed conversion of bacillary-positive state in up to 90% and cavity closure in up 76% of cases. Comprehensive analysis of treatment results in patients with complicated destructive pulmonary tuberculosis treated with alternative methods for medication administration was concluded by the Doctor thesis defended by S.S. Gavriliev "Chemotherapy of destructive forms of pulmonary tuberculosis using various methods of medication administration".

The year 2001 was the beginning of new phase in development of therapeutic departments. Disciples of S.S. Gavriliev and Z.E. Lineva (Fig.) make the staff of the Phthisiatry Research Practice Center and the pulmonary tuberculosis departments; they are followers of the followers of doctors from Moscow, the second generation of Yakutsk phthisiologists.

In today's epidemiologic situation that grows more complicated from year to year, the search for novel effective combination chemotherapy methods goes on. Gavriliev S.S. and Yakovleva L.P. proposed the rectal administration of ozone, potent antioxidant inhibiting free radicals, in patients with destructive pulmonary tuberculosis [7]. Gavriliev S.S. and Pavlova E.S. continued the studies on region-specific features of pulmonary fibrosis and proposed another treatment method for destructive pulmonary tuberculosis, which is based on potentiating effect of ultrasound on lydase and hydrocortisone, allowing their deep penetration to an area of local pulmonary fibrosis projected onto the skin surface of the chest, and leading to increased penetrance and decondensation of the connective tissue, essential for full healing of cavities [8].

Considering the currently existing epidemiological situation for tuberculosis in Russia and in Yakutia, phthisiologists are working on new methods for treatment and surveillance of drug-resistant tuberculosis of the respiratory organs. The most attention is paid to the problem of overcoming the drug-resistance of M.tuberculsois and to adaptation of the WHO tuberculosis control program to extreme environment of Yakutia. Four different specialty therapeutic departments are currently functioning in the State Budgetary Instution of the Sakha Repulic (Yakutia) Research Practice Center “Phthisiatry”. The doctors carry on the traditions laid by the founder phthisiologists, the pioneers of anti-tuberculosis service in Yakutia, and continue multidimensional research aimed at novel ways to improve chemotherapy effectiveness, based on region-specific patterns of adaptation processes during tubercular inflammation in the extreme north.

Professors Gavriliev S.S. and Lineva Z.E.

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