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To the Anniversary of Vladimir Ivashkin

Clinical diagnosis at the bedside always was, still is and always will be a criterion of a doctor's professionalism

In 2019, on the eve of Vladimir Ivashkin's 80th birthday, we conducted our first interview with him. Now, on the eve of his 85th birthday, Professor Ivashkin again kindly agreed to talk with us and share his thoughts, emotions and impressions about the key events of the past five years.

Professor, the COVID-19 pandemic has become the main vital problem of the past five years. This has never happened in the history of our generation and, we believe, yours. In December 2019, when there was information that a new virus had appeared in China, it was difficult to assume that it would spread throughout the world and affect almost all of us. But after a couple of months, it became clear that danger was no longer just "on the doorstep", but "has already entered our home". What is your view on this situation?

The question is very important. The COVID-19 pandemic was initially perceived by people following the scientific literature as a variant of a relatively small, brief outbreak of severe acute respiratory syndrome that had been reported several years earlier in China. Initially, what attracted attention was that it was accompanied by truly severe respiratory failure. Of course, clinics all over the world immediately became involved in this problem. And quite quickly, publications appeared in which, at that time relatively schematically, the phase pattern of the course of this disease was given.

Those international recommendations that were widespread at that time and taken from the experience of Chinese doctors, particularly the early prescription of antibiotics (for example, azithromycin), unfortunately, did not give the expected results. It became clear that this disease itself has various qualitative characteristics, from severe fulminant cases ending in severe respiratory failure of patients who were forced to transfer to controlled ventilation, to situations that were relatively easy.

It quickly became clear that the morphological basis of severe acute respiratory syndrome was lung damage. Moreover, the first morphological studies showed that this lung pathology included destruction of the alveolar wall, microthrombosis of the pulmonary vessels and interstitial inflammation.

High levels of pro-inflammatory cytokines IL-1, IL-6, and TNF-α were found in patients.

We then very carefully studied the clinical picture, and it turned out that it consisted of several phases: phase 1 — severe intoxication with damage to the respiratory system, detection of crepitus in the basal parts of the lungs on auscultation, and on tomograms — of different areas of lung damage in the form of ground glass, which concealed bronchioloalveolitis. Plus, there was a weak response to antibiotics. All this taken together led to the conclusion that the initial toxic phase of this disease is caused mainly by the massive introduction of the virus through the entrance gate of the angiotensin-converting enzyme receptor type 2 and the sharp stimulation of the immune system aimed at activating the inflammatory response. This could be interpreted as a protective reaction of the body, the scale of which exceeded the tolerance threshold of all body systems. Naturally, the question arose

that such super activation of the immune system requires protective measures. Therefore, we came to the conclusion that it is necessary to prescribe a universal factor that suppresses the excessive activity of the immune system, namely glucocorticosteroids. Unlike other medical institutions, our clinic abandoned the early prescription of antibiotics and began using dexamethasone instead. The results did not take long to arrive! Then, in fact, it became clear that in these patients, simultaneously with the activation of the immune system, the state of coagulation status changed significantly (as a response to a general severe condition), namely, universal hypercoagulation processes unfolded, which, in addition to the toxic effects of the virus and a severe immune reaction had an impact on systemic blood flow, leading to the development of microthrombosis and tissue ischemia. Therefore, the anticoagulant enoxaparin was added to dexamethasone therapy. Well, by this time, the first recommendations for prescribing anti-inflammatory interleukins for COVID-19 had already appeared.

Thus, a triad has been formed for the treatment of patients with COVID-19 — hormones, anticoagulants and anticytokine drugs. This led to a significant reduction in the mortality of patients in our clinic. When the Clinical Center of our University summed up the first results, and it was possible to compare the results of the work of different clinics, it turned out that our clinic differed significantly in its effectiveness, primarily in its much lower mortality rate. Sometime later, I found in the Lancet journal the results of the third phase of a clinical trial on the use of dexamethasone in patients with a new coronavirus infection in Britain. Our data and the data obtained by British scientists practically coincided. From this point on, information began to spread, and this triad for the treatment of COVID-19 was legitimized.

What about prescribing antibiotics?

Early administration of antibiotics in the first virological phase led to long-term consequences in a significant proportion of patients. During this period, many patients experienced diarrhea. At first it was incomprehensible to most doctors, but then it became clear that the intestines serve as an entry point for infection, the same as, say, the upper respiratory tract. That is, it was a direct virusotropic effect that did not require the prescription of any antibiotics, since, as we later saw, diarrhea tended to resolve on its own. At the same time, unjustified early prescription of antibiotics in the first virological phase led to the fact that a significant proportion of patients subsequently developed the second phase of diarrheal syndrome — antibiotic-associated diarrhea. In this group of patients, in approximately 70 %, we detected *Clostridioides difficile* infection, i.e. clostridial-induced colitis was added. And very often, patients who were on controlled ventilation experienced two competing life-threatening syndromes: respiratory failure syndrome, in which patients were transferred to artificial ventilation, and diarrhea syndrome, which exhausted and dehydrated them. Some of these patients developed pseudomembranous colitis, an extremely severe form of clostridial colitis. They, of course, had to be prescribed specific medications.

In addition, it was important to analyse the dynamics of clinical symptoms in patients. The first, virus-induced phase, was replaced by a phase of secondary bacterial infection, superimposed on the viral infection, typical signs of bacterial inflammation appeared, with the addition of chills, night sweats, sputum discharge, etc. But then the conditions for managing patients changed. The whole difficulty was that the doctors were extremely disadvantaged, wearing protective equipment. Therefore, the usual approaches and clinical methods for assessing objective status — percussion, palpation, auscultation — were practically excluded. The doctor had to apply his art and knowledge, focusing on the nature of the fever, the frequency of respiratory movements, heart contractions, and X-ray data, and compare changes in the lungs with the severity of the condition, assess the situation on this basis and resolve issues regarding management tactics. Then all this went into the already "habitual course": the prescription of dexamethasone, enoxaparin, in case of development of a bacterial infection — antibiotics, in case of increasing respiratory failure — transfer to controlled ventilation. In general, the whole process became clear and manageable.

Of course, we learned a lot from this situation. I think that in general the contribution of our clinic to the all-Russian understanding of patient treatment tactics was highly appreciated. It is no coincidence that three of our heads of departments: Natalya Kokina (the Head of the Pulmonology Department), Manana Skhirtladze (the Head of the Cardiology Department) and Olga Kiseleva (the Head of the Resuscitation and Intensive Care Department) were awarded the Order of Pirogov. And we are very proud of that!

The specialists who were initially categorically against hormones and discussed this matter with you a lot, probably later admitted that they were wrong?

There were many objections to the use of hormones, but the rationale for this was very primitive: why prescribe hormones, after all this can expand and deepen the infection. Of course, these

objections stemmed from misunderstanding of pathogenesis, the nature of the disease that we encountered.

When the doctors at our Clinic started getting sick in the first wave, and they were seriously ill, was there any fear for them? Or were you confident that our colleagues would cope and be able to help them?

Of course, there was, there was anxiety… (*thoughtfully*). But, on the other hand, they were not the very first people to get sick. Our Clinic already had experience, and, most importantly, it was clear that in the case of the most severe course, we could use in time everything that we had then. I didn't want to get sick either. It happened quite often that time — one dies, another dies, people my age, younger than me, a lot of people died. We are not talking about fear here… there was no fear, there was anxiety, and at the same time, hope that this would pass you by.

Did you feel that at that moment the whole Clinic and Department united?

I must say that our Clinic and the Department responded like the rest of medical community. Those who found themselves face to face with that difficult situation, of course, rallied. Both the Department and the Clinic really came out as one strong unit. They handled it well! I was very proud then and am proud now of all the awards that our employees received! The Clinic was celebrated, our successes did not go unnoticed. And we demonstrated our scientific achievements in publications. We have published about 30 articles on COVID-19 in leading Russian and foreign journals.

The wave of COVID-19 has passed, but new syndromes associated with this infection have emerged.

Yes, the story with the coronavirus infection is not over, and currently the next problem is clearly emerging — the so-called long, or protracted, COVID. Initially, long COVID was described as a complex of symptoms indicating involvement of the central nervous system, weakness, fatigue, decreased exercise tolerance, myalgia, and manifestations of peripheral neuropathy. But it is now becoming clear that long COVID is a much more serious problem. A number of diseases currently occur either with an altered clinical picture or maybe these are new syndromes that are caused mainly by the residual persistence of the virus or remnants of the virus, its spike proteins. This problem is probably becoming wider, and more and more publications appear on seemingly classic diseases that acquire an aberrant course.

And here I can refer to examples from our Clinic. A female patient with chronic liver disease, steatohepatitis, who, after suffering a new coronavirus infection, developed severe cholestatic syndrome, which had external signs of obstructive jaundice — high bilirubin, discoloration of stool, dark urine… Biopsy verified disappearing bile duct syndrome. This patient is being monitored. In our Clinic, we observed two cases of acute protein-losing diarrhea, in which patients suddenly became ill with severe diarrhea that was not relieved by any known means. Then pathomorphologists, in particular, Professor Evgenia Kogan, using histochemical analysis discovered coronavirus markers in their intestines. A patient with myocarditis was admitted to the Cardiology Department and died from severe cardiovascular failure, and spike protein was detected in his myocardium. The spike protein of the virus was detected in the lung tissue of a patient with an unusual, rather rare form of diffuse sarcoidosis, with the presence of multiple sarcoid granulomas occupying both lung fields. Thus, doctors now need to be prepared in cases of persistent, severe, intractable course of seemingly habitual diseases, not to forget about the possibility of the continuing antigenic effect of coronavirus proteins contributing to such a change in the form and severity of the disease.

The whole world was eagerly awaiting the arrival of a vaccine against COVID-19, and, at the same time, there were strong protests against vaccinations. What is your opinion about the created vaccines?

After the end of the acute phase of the pandemic and a significant reduction in incidence, the world breathed a sigh of relief. But then it became clear that vaccination, especially with RNA vaccines, did not pass without a trace. During the height of the pandemic and after, it became clear that RNA vaccines were causing side effects. Which ones exactly? In young people, these are mainly cardiovascular complications: carditis in various forms, pericarditis; also acute thrombotic thrombocytopenic syndrome, which occurred with widespread micro- and macrothrombosis and was complicated by cerebral hemorrhages.

As for the Sputnik vaccine, it has been studied in great detail, for example, in Argentina. And out of multimillion-dollar statistics, only two cases of the development of thrombotic thrombocytopenic purpura were noted. Cases of carditis after the introduction of Sputnik were not recorded anywhere at all, neither in Russia nor in more than 60 countries where this vaccine was used as the main one for immunization of the population.

Now the scandal in the West is flaring up more and more. The fact is that RNA, as a vaccine matrix,

is not capable of targeted transport to the desired cellular organelles. Some foreign researchers believe that administered RNA vaccines can cause various pathological reactions over many years.

Therefore, at present I cannot take a definite position for or against, but in the West the number of opponents of vaccination is growing sharply. True, there are no publications confirming the fear of such a vaccine, presented by biologists or researchers. Therefore, it is difficult to say whether this is reality or some kind of opposition based on other principles.

Your personal opinion: should people get vaccinated?

I get vaccinated! I administer the influenza vaccine every fall, and I also use the pneumococcal vaccine. I received Sputnik twice, with a two-week interval. After the first dose of the vaccine, I had a very low antibody titer; I am a weak reactant. But after the second titer rose. Of course, the vaccine provided some confidence.

In 2020, a new textbook on propaedeutics of internal diseases was published. The previous textbook, from which we all studied, turned 50 years old this year and it was clear that the rules of percussion, palpation and auscultation would not change in 50 years, but what was described in that textbook in terms of methods of laboratory and instrumental diagnostics and much more, outdated. And now its second edition has already been published. What do you think modern students need in general now? They are different from us; they cannot be interested by just a book.

I'm afraid I'll turn into a grump if I compare the modern student with the students we were. For as long as humanity has existed, older people say (*laughs*) "the grass was greener before", etc. But, nevertheless, the world goes on, lives, prospers, every generation has its own stories of Romeo and Juliet, every generation have their own Anna Karenina. The same thing happens in all generations. As always, students need to instill a love of work. Of course, this is a very difficult process. Love for work is formed in the family. But the teacher must also show by example that it is necessary to WORK.

What do students need? Students need knowledge, deep immersion in literature, in culture in general. Because a doctor must be immersed in culture. I don't know how to implement this... I am a regular visitor to the conservatory, the Tchaikovsky Concert Hall, opera houses, and I don't see young people there, or I see very little of them compared to middle-aged or older people. At first this annoyed me, and then I began to remember who, what kind of audience I saw at the Covent Garden in London, at the Vienna and Milan Opera? And there, too, the middle-aged and older audience dominates. But there are a lot of young people at jazz concerts, they go crazy about jazz. In this regard, I conclude that everything has its time. Everyone has the same thing: they get married, have children, and when this happens, a person changes — they need to be an example for their children, and then they begin to understand that being an example for kids means demonstrating their own attitude to culture.

As for knowledge — I think that if a student or a doctor does not have a goal setting, if they do not formulate some tasks for themselves that will have to be solved in the future, then it is very difficult to make them work and study the subject deeply. I can give you this example: at the Military Medical Academy there were teachers who simply became an absolute example for me. My teacher Evgeniy Gubler, a pathophysiologist, literally infected me with a love of science. This was my goal setting.

In general, many things influenced me personally. In my youth I was fond of Remarque. There is a character in his novels — Doctor Ravik, who attracted my attention. This is a very interesting character who has always been with me. Or, for example, Archibald Cronin's novel "The Citadel", which is about an infectious disease doctor.

How to get a student to work? There is an endless change of different education systems presently. You, young teachers, have probably already felt this change. Does it evoke positive emotions in you or not? There was the general, in my opinion, very good, solid Soviet education system, where there was enough of everything. Then they decided to join the Bologna Convention, which is completely alien to us and does not have the necessary justification. And now they are trying to return traditional approaches to education. Our country, unfortunately, is going through the revolutionary path of development that began in 1917 in the educational system with a certain lag and brought innumerable, immeasurable suffering. I think that these rapid changes in the education system, in secondary and higher schools, are akin to these revolutionary motivations and movements and, in all likelihood, Russia will still need some time to find a stable middle ground position on these issues.

Returning to the question about the textbook. What role does a textbook play in a modern school? You know, I can refer to foreign experience in this regard. I think that no one will have any objections to the fact that European schools of higher education, in particular British, French, German, and American, certainly, with all their shortcomings, have enormous attractive power. They produce results. One could argue, of course, that the

effectiveness among graduates of these schools primarily belongs to talented migrants who come there and assimilate in that atmosphere, find a new homeland for themselves, etc. If we compare educational literature, then their textbooks are the best and most effective textbooks in the world. And they are used by millions of students, they are the basis for education. It seems to me that we don't need to "turn up our noses", we need to follow the example and create textbooks that provide the same amount of information and in the same form as these outstanding publications.

Therefore, when I created the textbook, I tried to take the best foreign manuals as an example. Of course, I used a lot from my experience, which I gained while studying at the Military Medical Academy, and during my forty years of work as a military doctor. And the clinical component of this textbook is its most important part, since regardless of the remarkable achievements, regardless of the fact that high hopes are now placed on artificial intelligence, physical diagnosis of diseases at the patient's bedside and, especially, in military field conditions was, still is and will be an integral part of serious doctors.

A year ago, your scientific school was recognized as the best in the competition of Innovative Schools of Sechenov University. What does a scientific school mean to you?

I never asked myself whether I created a scientific school or not, do I have one? Of course, under my leadership, an endless number of candidates and doctors of science defended themselves, some of my graduate students and employees achieved truly outstanding results. Among them are already heads of departments and laboratories, deans, vice-rectors, rectors of medical universities, directors of research institutes. During this time, many of those who studied under my leadership and worked with me went beyond the department and clinic. We have founded several scientific societies that are well known and popular. We have one of the most famous specialized gastroenterological journals. Indeed, we managed to do a lot. Is that a school or not? And in general, is it necessary to somehow combine all this into the concept of a scientific school?

A scientific school is sometimes like a kind of cap that is put on by a professor whose 3–4 graduate students have defended their PhD theses. Then, at the next anniversary, someone always says: "Professor, you created a scientific school". And that scientific school has only a few dissertation candidates. Then again, there was Hippocrates, he had many students, there was Aristotle, who also had many followers. The school of Hippocrates — does it exist? Or does Aristotle's school? This question is impossible to answer.

My outstanding teacher was Academician Alexander Ugolev, the creator of the doctrine of parietal digestion, Nobel Prize nominee. He was the supervisor of countless candidate and doctoral dissertations. More than 30 years have passed since his death. Has his school survived or not? I don't know. Because there are practically no works devoted to parietal digestion at present.

When a person comes to a graduate school, they receive a topic and a supervisor. And this is the key point! What is a scientific supervisor like? This is a very serious question! (*nods meaningfully*). Because the image of a leader either destroys a graduate student, or, on the contrary, creates from them a person who further works independently, sees goals, tasks, etc.

Therefore, the concept of a scientific school must be treated very carefully, and there is no generally accepted definition of it. After all, the basis of what people want to call a scientific school is the methodology used by the founders of this entire circle. Methodology of the process of teaching students, methodology of the process of improving the quality of doctors, methodology of conducting scientific research and achieving the most significant results. And therefore, when we talk about a scientific school, we should ask ourselves, what methodology underlies the work of this leader? How clearly can it be formulated? And if these principles that guide him can be formulated and designated in the form of a certain code, then, probably, it will be possible to talk about a scientific school. And if this cannot be done, it is unlikely that such a scientific school exists. So, try to outline my methodology, formulate the scientific principle that guides me in my work with graduate students, doctors, and you (teachers). Will you be able to do this? If you can do that, it means that my school exists in some form. And if you cannot, then what kind of school is this…

In February of this year, we celebrated the 150th anniversary of the Clinic and the 160th anniversary of the Department. Of course, it is difficult to predict in advance what will happen. But still, what would you like to see the Department and Clinic like in many, many years?

I want to say that working at a department and clinic that has a history of 160 and 150 years is very attractive, it warms one's heart. You are not a neophyte at the Department, which arose 10 years ago, but you are a follower of a large galaxy of very talented professors who proved with their work and their results the need for the existence of both the Clinic and the Department. After all, they exist not because someone wants them, but because

they prove their necessity! Consequently, the task of every leader is to prove the necessity of this existence. This can be done in different ways. The worthiest and having the longest continuation is the principle of achieving results in teaching students, science, and treating patients. Another principle is to be a "social climber" and acquire new and new contacts with various higher and higher bosses, and benefit from this, but at the same time pay less attention to deep work. Some people can combine both. Vladimir Vasilenko was both a wonderful doctor and a scientist, and at the same time his experience, including the experience of the Chief Therapist of the fronts during the Great Patriotic War, made him attractive in terms of invitations to high positions.

The project "National College of Gastroenterology, Hepatology" created by you has existed for more than one decade. What are the prospects for its development?

Our Gastroenterology College is not a project invented by me. The first Workshop in the field of physiology and clinical gastroenterology was created by my teacher A. Ugolev. It was an amazing event for which he brought us together once every two years. The workshop lasted two weeks, all lectures took place in Kaluga, in one of the hotels on the banks of the Oka. It is difficult for me to understand why he, a native Leningrader, chose Kaluga. We all lived in this hotel and were completely immersed in this extraordinary atmosphere. It was a great honor to give lectures there, and by the way, they were two-hour lectures, academic ones. I myself was a lecturer at three such workshops.

And in fact, the idea of our College came to me from that workshop of A. Ugolev. And then, when trips to foreign congresses began, we saw two-day Schools that preceded the scientific session, they were also distinguished by their exceptional content and depth of material, and the skill of conveying this material to the audience. In addition, at the time when I moved to Moscow, there was no comprehensive methodology for immersion in the problems of gastroenterology in our country. And this served as the driving force for the creation of the College. I remember the first workshops of the College that were held here, they drew big audience, people came from all over the country. This enthusiasm of the participants, of course, created an understanding that the workshops were urgently needed. From that moment they commenced. What is the attractiveness of the workshops? The fact is that they are neutral; there is no desire on the part of the lecturer to highlight any aspects, individual achievements of certain laboratories or departments. Lecturers are instructed to talk about the most recent, interesting and important achievements in the issue they are talking about. The history of the College makes participating in its work attractive and very honourable. This is the basis of the success of our National College of Gastroenterology and Hepatology.

We know that you are an expert and connoisseur of music, opera and ballet. What phenomena in these types of art have made the strongest impression on you over the past five years?

Once I watched the opera "Sadko" by Rimsky-Korsakov at the Bolshoi Theatre, where the role of Volkhova was performed by Aida Garifullina. I was amazed by her talent! In the Milan Opera's production of Rigoletto, Olga Peretyatko performed the role of Gilda. I considered myself an absolute supporter of our opera diva Anna Netrebko, she remains my idol, but these singers made a very strong impression on me. Hibla Gerzmava continues to shine in the role of Norma at the Stanislavsky and Nemirovich-Danchenko Theatre. She is our best Norma!

All shows of the Bolshoi and Mariinsky theatres are outstanding achievements. And they, of course, are head and shoulders above all the ballet performances of the Paris Grand Opera or London's Covent Garden. The advantage is absolute. The same applies to any opera performance — it is something outstanding.

I was a big fan of dramatic theatre when I lived in St. Petersburg. And when I moved to Moscow, I also began to actively go to theatres here. But after the Bolshoi Drama Theatre named after G.A. Tovstonogov, its absolutely fantastic troupe, Moscow theatres did not win my heart. And then, musical images, in my opinion, are much deeper than dramatic images.

I really like the programs to which talented children are invited — "The Blue Bird", "The Nutcracker". When I see these little ones playing Mozart absolutely brilliantly, it makes me truly delighted! How do we differ from the West? What do they do? They invite people from everywhere. There are 200 nationalities in Russia, they are all mixed. The Russian gene pool is one of the richest gene pools. And from this gene pool talents are born. All foreigners say how beautiful the women in St. Petersburg, Yekaterinburg, and Russia in general are. And it is indeed so.

As for literature, I read all books of Tana French. This is an Irish writer in the detective genre. Well, this is in my free time, to keep up with the modern world. You should also try reading Tana French — you will like her works!

But when something gnaws at me, I read the Old and New Testaments. Everything can be found there, the answer to any question.

What are your plans for the next 5 years?

You know, Leo Tolstoy ended each day's diary entry with these letters — "I.I.A." — if I'm alive. The first and most important thing is to stay alive! Secondly, I hope that I have enough strength to maintain contact with the Department and the Clinic. Although some may say that at my age I need to rest, I can't imagine rest without a team of doctors, without doing science, without deciphering diagnoses. People in our "trade" need flexibility of intellect, not just one or two memorized roles that can be automatically reproduced. We need flexible, voluminous memory, a lively mind capable of perceiving new things, because old age begins with fatigue from information. If a person wants to learn, and learn in different forms, reads, listens, teaches, then this is a productive mind, it provides the basis for the continuation of social life. Once I tried to count how many times I switched to different topics with different people during the day, it turned out that it was a lot of times. And the memory rushes about, it must extract something from one compartment, then from another, from a third… if this movement of memory persists, then you are alive, energetic, active, and then you are interested, and people are interested in you. Therefore, the main task is to maintain flexibility, the ability of brain activity to switch from one section of knowledge to another and retrieve facts and data that are necessary from the depths of memory.

It is also very important to know that patients, students need you. We need you.

The person himself does not realize this, being wanted. I don't realize it.

We assure you that we need you!

To be honest, I don't perceive myself as an absolutely necessary person. If I perceived myself this way, then perhaps I would behave differently, maybe I would have more arrogance, more rigidity, more "showing off". I don't feel it. And I quite clearly feel the need for a team and for work. And if I go on vacation for a week, then I slowly become sour, I start thinking "why did I leave? "did I feel bad there?" This is not slavery to habit or to duty. This is the need for creativity!

The interview was prepared for publication by Natiya L. Dzhakhaya, Alla V. Sedova, Oxana Yu. Zolnikova

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