NOTES ON THE ROLE PLAYED BY MICROBIOLOGICAL FACTORS IN THE OCCURRENCE AND COURSE OF SCHIZOPHRENIA

L. Ivanova, G. Kaprielian, V. Ivanov, P. Stamboliev. | V. Gardevska, A. Panayotova, H. Dimitrova, L. Nicheva

The issue of the correlation between macro- and microorganism in schizophrenia is not a recent one. It is by no means confined to the infections etiology of the disease alone, in the narrow sense, since it deals with the determination of the complex role (primary or secondary) played by microorganisms in the course run by schizophrenic psychosis also as an eventual provoking and supplementary factor. In a broader aspect, it is converted into a discussion of the interrelationship existing between exo- and endogenic factors (A. G. Naku, 1961).

In psychiatric literature the problem of the direct role played by the infectious factor in the occurrence of schizophrenia has been similarly repeatedly raised. After rejecting the concept of Z. Marchand (1939) and of other authors about the tuberculous etiology of schizophrenia, nowadays attention is called to a variety of possible contributing causes of bacterial, mainly Escherichia coli, streptococci etc (H. Clamde — 1926, H. Baruk — 1953, A. S. Chistovich — 1954), and viral origin (V. M. Morozov and M. A. Morozov — 1954, G. Scarlatto and P. Mastrogiovanni — 1956, P. D. Mastrogiovanni — 1958). Definite data on the above issue may be also found in our preliminary report (V. Ivanov et al — 1965). Indirect evidence of a possible viral infection has been demonstrated through obtaining cytopathic effect after the passage of serum and liquor from schizophrenic patients over cell cultures (M. E. Vartanian and R. I. Rapoport — 1963), and after "infecting" chick embryos (the same authors: G. Uzunov, G. Mitov — 1959).

The question of the role played by immune processes in schizophrenia is likewise partially related to the above problem, although lately it has been developed independently from autoimmunogenesis standpoint. A. great number of literature reports on the issue have been already published (S. F. Semenova — 1961, K. N. Nazarov — 1961, Y. Stoimenova — 1961, V. S. Glebov — 1963, N. I. Kuznetzova and N. N. Popova — 1963, L. A. Stukalova — 1963, V. A. Kornevskaya and E. V. Miheeva — 1963, A. P. Chuprikov — 1964 and 1966, V. B. Ivanov — 1968, Y. I. Hadzhieva and V. H. Valchanov — 1968 and others). Reference is made to the antigen-antibody reaction, demonstrated through the reaction for complement fixation, or to skin tests with brain antigen introduction, as well as — in isolated cases — to anaphylactic and desensibilization reaction after Silber. The occurrence of the reaction following intracutaneous introduction of "antischizophrenic" antibodies i reported in a few publications only (H. Kobayashi — 1956, S. Kolzumi e$^{s}_{t}$

al — 1958, L. T. Ivanova — 1970). The so-called AVB reaction (agglutination of virus-carrying bacteria) occupies a rather special place in this group of researches (F. N. Chubinetz and R. M. Shilman — 1957, G. J. Malis — 1959, V. Ivanov et al — 1961 and 1965, 1967, 1969 a and 1969 b, Z. Stefanova et al — 1963).

The immune processes in the organism of schizophrenic patients have been also studied by means of paper electrophoresis and immunoelectrophoresis (L. I. Lando — 1959 and 1968, K. Milanov — 1964, V. A. Korenevskaya — 1967, P. Stamboliev — 1969, P. G. Spilimergo et al — 1972).

It is the purpose of this work to carry out a complex study on a more extensive clinical material, and to compare the data from clinical, clinico-laboratory, bacteriologic, virologic and some immunologic investigations.

Material and Methods

The study covers a total of 213 schizophrenic patients (109 in the acute stage, and 104 in the stage of chronification). The acute patients are from the case material of the Clinical District Psychiatric Hospital in Varna, while the chronic patients are from the District Psychiatric Hospital in the village of Tzarev-Brod (district of Shumen). Thirty one patients with various mental affections (neuroses and chronic alcoholism), as well as one hundred clinically healthy individuals, aged 20—40 years, were used for control purposes.

The bacteriologic and immunologic methods included investigation of nasal and laryngeal secreta using routine microbiological techniques (cultivations in glucose formate broth and blood agar). Using the diffusion method[1] the antibiotic sensitivity of the isolated pathogenic strains against twelve of the antibiotics most frequently employed in practice was determined. In addition, in part of the patients investigations of Listeria monocytogenes in the laryngeal secretion and feces were performed. Listerial Widal is also studied with the serum of patients. The study of antistreptolysin titer after the method of Köhler with streptolysin (0) — produced by the Center of Infectious and Parasitic Diseases — was likewise included in the complete set of bacteriologic and serologic methods.

Virus study was carried out by means of serologic reactions, cell cultures' infection, inoculation of chick embryos and laboratory animals, and immunofluorescent microscope investigations. Swabs from the rhinopharynx, feces and blood in the acute stage and during convalescence (remission) for patients in the acute stage, and usually a single time for those in the chronic stage of the disease, were used as material for examination. The serological study included reaction for complement fixation according to Mayer in cold, making use of the following antigens: Adeno — common, ECHO — common, Mycoplasma, RS, Coxsackie — common antigen. The antigens for Adeno and Coxsackie, groups A and B, were obtained from the Chair of Microbiology and Virology of the Medical Faculty — Varna, on cell cultures from human embryonal kidney (HEK) and laboratory animals (for Coxsackie) through threefold freezing and thawing, and subsequent centrifugation at 3000 rpm for 20 minutes. Antigens for Mycoplasma and RS were obtained from the virological

[1] The results of the antibiogram are not submitted in the present report. They will be relevant for future practical conclusions in the treatment of patients.

laboratory of the Hygiene-Epidemiologic Institute in Plovdiv. The sera underwent beforehand treatment for 30 min at 56—58° CO_2 for thermolabile and thermostabile inhibitors' removal. For the reaction 4 U antigen and 2 U complement were employed. Titers 1; 10 and higher were accepted as positive.

The sera were serologically studied for influenza and parainfluenza according to the micromethod of G. V. Takatsy (1955), making use of the following diagnosticums for hemagglutination-inhibition reaction: influenza A-Shkliaver, A_1 -Klim, A-Sf/57, A-Engl./64, A-HK 1/68, A-Engl. 42/72, A-Vn/73, V-HK 173, S_{1233}, antigens PG_1, PG_2 and PG_3. The influenza diagnosticums were obtained from the Influenza Center — Sofia on chick embryos, whereas those for parainfluenza — on cell cultures.

In 50 patients in the acute stage of schizophrenia (I attack) and in 50 chronic patients heterohemagglutination reaction after P. Bunel was performed, accepting as positive the reactions with antibody titers 1:64 and higher.

To isolate viruses 10 to 12-day-old chick embryos, monolayered trypsinized cell cultures (HEK) and laboratory animals were infected with swabs and feces from patients in I attack. The material was previously treated with antibiotics (penicillin and streptomycin), whilst for chick embryos' infection the material underwent treatment with guinea pig erythrocytes.

Cell cultures subjected to primary trypsinization were obtained after the method of J. S. Jounger (1954). Three consecutive passages were carried out. Typing of isolated viruses was accomplished through VNR using type specific sera, made in the Chair of Microbiology and Virology — Varna and in the Institute of Virology — Moscow.

To isolate Coxsackie-viruses in particular newborn white mice were subjected to subcutaneous and combined (subcutaneous + intracerebral) infection. Up to three passages were performed and then the isolated viruses were typed on a model of newborn mice using type-specific group antisera.

Immunofluorescent study was made with conjugating sera to influenza type A virus, influenza type B virus, parainfluenza viruses, adeno- and RS viruses.

Immunoglobulins were investigated through immunodiffusion method for comparative analysis of the blood serum antigenic components according to a personal procedure (P. Stamboliev — 1966). Monovalent antisera, obtained from the firm Boehring Werke A. G., Marburg, were applied, and owing to their specificity electrophoretic separation became unnecessary. The technique of microimmunophoresis according to M. Iomtov (1964), representing immunodiffusion in agar medium with veronal buffer at pH=8.2, served as a basis of the modification described.

The study of serum proteins was performed with paper electrophoresis and photometric recording.

Results and Discussion

In analyzing the clinical picture of the affection, we were guided first and foremost by the pathokinesis and by the stage of the morbid process. The patients in the acute stage were divided in patients with first attack (62 cases), and patients with subsequent attacks (47 cases). Out of the patients witht first attack the psychosis had an acute onset in 29, subacute — in 25, and i. was a matter of a slow and gradual process without a clearcut onset in eight

In the latter group of patients no assignment to the respective pathokinetic form was made since in the beginning of the attack this was not always possible. Of the patients with recurrent attacks, 28 were classified with the periodic, and 18 — with the paroxysmal-progressive type. The patients in chronic stage were distributed among the following pathokinetic forms: 14 — periodic form (of very long standing, multiple recurrent attacks and already present signs of personality degradation), 27 — paroxysmal progressive, and 51 — running a continuous course; in twelve patients the pathokinetic form did not lend itself to precise determination.

Insofar as syndromologic characteristics is concerned it is made up of the "paranoid group" syndromes in the great majority of cases, namely: paranoid, hallucinatory-paranoid, paranoial and paraphrenic. Catatonic manifestations were observed in isolated cases only, and in some of them (as a rule, in periodic insanity) — affective and oneiroid manifestations as well. By the way, some of these characteristics will be referred to later in the text.

Patients studied in the acute stage and in the active period of psychosis (totalling 109) display some clinical and mainly paraclinical data pointing to general somatic changes. Thus the rise in temperature (a single time or, more frequently, repeated) was registered in a total of 40 patients, with febrility being recorded in 18, and subfebrility — in 29 patients (in 7 either type was present). In the group of febrile patients the cause of high temperature was clarified in 13 cases, and it was supposed in one. Of the remainder where high fever was present at different periods of the hospitalization, one episode was clarified (one patient), and in another two a body illness was supposed. However, most of the cases with subfebrility remain unclarified: in this group the cause was established in five cases only, and supposed — in three; of the patients with repeated subfebrile episodes the cause was discovered in three, and presumed in two. Our data are in agreement with those reported by K. Milanov (1964) in the "first group", differentiated by him on the basis of clinico-laboratory data during the primary, acute attack of schizophrenia. However, in our series temperature rises are also recorded in patients with subacute onset during the first attack, and during the recurrent paroxysmal attacks in the acute stage of the disease. In the inactive (convalescent) stage an increase in temperature was noted only in one patient. The impression is that unlike the results in the cited work of K. Milanov (1964), leukocytosis according to our material was rarely met with — in eight patients only. Yet, an accelerated erythrocyte sedimentation reaction was very often recorded (in 36 patients, twice during the active period in the average). The circumastance that a speeded up sedimentation wasn't established in any of the patients in the inactive stage points to the fact that this particular phenomenon is related to the dynamics of the basic illness (Table 1).

Table 1

Temperature, ESR, proteinogram of patients in the acute stage

	T° (patients %)	ESR (patients %)	Reduced albumins (patients %)	Increased — globulins (patiens %)
In the beginning of attack	17.65	15.69	34.39	37.25
In convalescence (remission)	0.99	0	17.81	23.29
Reliability of the difference in the beginning and at the end of attack	$p \leqslant 0.001$	$p < 0.001$	$p \leqslant 0.02$	$p < 0.05$

Definite changes are observed in the proteinogram of patients. Here the typical changes comprise: increase in the amount of total protein (20 reactions in 16 patients), reduction of albumins (42 reactions in 35 patients), increase in globulins: of alpha$_1$ — (25 reactions in 22 patients) and alpha$_2$-fractions (13 patients), and particularly of gamma globulins (46 reactions in 38 patients). At the same time, beta-globulin fractions show a tendency toward reduction (20 patients). In the inactive stage (convalescence) where all patients are studied for the first two indicators, and 73 — for the remainder, a reduction in the number of cases with decreased albumins as well as of patients with increased albumins is observed (Table 1).

The immunodiffusion method is applied to 66 patients of which 29 are examined twice in the beginning of the attack, and 32 — in the recovery period. The overall changes in the acute stage are shown in Table 2. During the remission a reduction in the number of patients with increased immunoglobulins is recorded (not indicated in the Table), although it is reliable only in terms of the total number of increased fractions in patients examined twice each- in the beginning and at the end of the attack ($p < 0.05$).

Table 2

Changes in Immunoglobulins by the Type of Fractions

	Increased	Decreased	Total number with changes	Without changes
d_2M	19	2	21	41
IgA	16	6	24	33
IgM	8	3	12	50
IgG	11	1	12	50
Total fractions	54	12	69	179
Total patients	35	11	46	16

Table 3 illustrates the changes in immunoglobulins by the number of fractions (IgA, IgM, IgG) without differentiation of the latter. Here too a reduction in the number of increased fractions is noted at the end of the psychotic attack — in remission (not indicated in the Table), with the difference being reliable only in terms of the multiple changes (more than one increased fraction per patient).

Table 3

Changes in Immunoglobulins by thd Number of Fractions
(without alpha$_2$M)

	Increased (patients)	Total number with changes (patients)	Without changes (patients)
1 fraction	22	30	—
2 fraction	7	9	—
3 fraction	6	7	—
Total number of patients	35	46	16

In Table 4 the changes in immunoglobulins during the acute stage, convalescence and in mentally intact controls are studied comparatively. Between

Table 4

Increased Immonoglobulins (without alpha$_2$M) in Acute Stage, Convalescence and in Mentally Intact Controls

	Acute stage (No of fractions)	Convalescence (remission) (No of fractions)	Controls	Reliable difference between % correlation in patients+healthy indiv.
IgA	8	5	5	
IgM	4	3	—	
IgG	6	5	—	
Total number of fractions	18	13	5	
% of fractionS	20.69	14.94	2.(7)	p<0.001
Total number of patients	14	12	5	
% of patients	48.29	41.38	3.(3)	p<0.001

mentally intact and schizophrenic patients both in the stage of attack, and in remission (convalescence), reliable differences are established in terms of the percentages of increased fractions, and of patients with augmented immunoglobulin values alike.

On analyzing the results of the microbiological study, emphasis should be laid on the fact that only 18 patients in the acute stage of schizophrenic psychosis, and 23 — in the chronic stage failed to show variations from the normal values. Yet, if the conditionally pathogenic flora is excluded, the difference between the two stages of the disease becomes considerable: pathogenic flora is established in 77.06 per cent of the patients in acute stage, and in 55.77 per cent of those in chronic stage (P <0.001).

Combined infections are rather frequent, particularly in the acute stage— 35 patients, with a combination between viral and pathogenic bacterial flora being present in 18 cases, viruses with Mycoplasma pneumoniae and Rickettsia Burneti — in 9, the latter two plus bacteria — in 5, and simultaneously with viruses plus bacteria — in three. Moreover the higher incidence of mixed infections in acute, and up to a certain extent, in subacute onset of the first schizophrenic attack, as well as in periodic course of the recurrent attacks is impressive.

Of the microorganisms found in the course of bacteriologic study of patients in acute stage of schizophrenia, Staphylocccus aureus and Bact. proteus are considered as pathogenic, while Escherichia coli, Candida albicans and Staphylococcus albus — as conditionally pathogenic. It should be added right away that here the frequent detection of Staphylococcus aureus is most essential (in 40 investigations of 31 patients), whilst Bact. proteus is established in isolated cases only. Among the conditionally pathogenic flora, Candida albicans is present quite often (37 positive finds in 28 patients). The increased antistreptolysin titer (AST) discovered is of particular interest in this respect (42 positive finds in 25 patients). The study of 66 patients with listerial Widal yields zero titers in 59.09 per cent, and low titers — in 40.91 per cent which ruled out the diagnosing of listeriosis. The results in the beginning of the psychotic seizure show a considerable fall during remission: 14 St. aureus finds in nine patients (p <0.01), and 13 AST finds in three patients (p <0.001). Furthermore, it is impressive that although the titers established in remission are generally lower (just half of them are above 250 U), while in the acute stage AST>250 U is recorded in nearly $^3/_4$ of the patients, the antistreptolysin titer, followed in the same patients, did not show noteworthy changes parallel to the improvement of the clinical picture: a decrease — in seven patients, an increase — in six, and unchanged level — in three.

The search for antibodies against viral infections through the complement fixation reaction (CFR), and for influenza — through the hemagglutination-inhibition reaction (HAIR) yielded positive results in the postacute period (and 9 in remission) relative to influenza viruses — accordingly 14 (9); Coxsackie viruses — 9 (1); with common antigen against ECHO-viruses — 8 (1); parainfluenza$_1$ — 4(1), RSV — 3 (1) and ornithosis virus — one. In isolated cases ECHO-viruses are cultivated on tissue culture, influenza viruses — on chick embryo, and coxsackie A and B viruses — on laboratory animals. The virus agent was confirmed simultaneously serologically and by one of the other methods — in a total of nine patients. Through virological and serological investigations positive results were obtained in a total of 52 patients in the acute stage, with mixed viral infections being established in nineteen of them. Most frequently the antibodies established were against the influenza strains AHK $^1/_{68}$ — eleven, next ranking A ENG 42/72 — seven, VSE/59 — four, B(MAS) and A/SF$_{57}$ — three each etc. (As a rule, in the same patients antibodies against several strains were simultaneously demonstrated). Besides that in 11 (6) cases antibodies were established against Rickettsia Burneti, and in 7 (2) — against Rickettsia Burneti. Heterohemagglutination after Paul Bunel was made in fifty patients with positive results in four of them.

In comparison with the data obtained in the acute stage of the illness, the findings in the chronic stage are much scarcer. Thus the rise in temperature, both febrile and subfebrile, was observed in one patient only. The persisting speeded up ESR is impressive — 93 reactions in 33 patients, while in three cases the reaction was accelerated throughout the entire period (for many months) of hospitalization in the clinic for chronic patients. Analogical changes were likewise observed in the proteinogram: reduction of albumins (22 patients), increase in alpha$_1$ (6 cases) and alpha$_2$ (7 cases), increased gamma-globulins (29 observations). The percentage difference between the above cited results is submitted in Table 5.

Once again attention is called to the persistent high antistreptolysin titer (increased in 35 investigations performed in 23 patients).

Table 5

Acute and Chronic Stage Proteinograms

	Acute stage	Chronic stage	P
Patients with reduced albumins (in %)	32.11	21.15	<0.05
Patients with increased α-globulins (in %)	20.18	5.77	<0.01
Patients with increased α-globulins (in %)	11.93	6.73	>0.05
Patients with increased γ-globulins (in %)	34.86	27.88	$\geqslant 0.05$

The bacteriologic finding in the chronic stage of the disease is somewhat scarcer: St. aureus is found in 20 patients, Bact. proteus — in three, Listeria monacytogenes strain 25 85 (isolated from pharyngeal secreta) — in one. Of the conditionally pathogenic flora, Candida albicans is met in 16 patients, and St. albus — in eight. One is impressed by the rather frequent isolation of E. coli (14 patients) which might be explained by the heavier contamination in chronic patients. Increased antistreptolysin titer was observed in practically the same percentage as in acute patients (23.08 in chronics against 23.03 in the acute stage), but in the chronic patients the lower values show a clearcut predominance: 19 patients with AST-250 U, and only 6 — with AST >250 U.

Particularly marked is the difference in viral investigation findings between the patients in acute and chronic stage: positive results, as already mentioned, were obtained only in six patients against 52 in the acute stage ($p < 0.001$). Here only 3 cases of virus Coxsackie, 2 — adenoviruses,and ECHO-virus and influenza virus — one each were isolated. In two of the patients it is virtually a matter of a mixed virus infection with Rickettsia Burneti and Mycoplasma pneumoniae. Mycoplasma alone was isolated in one patient. Heterohemagglutination according to Paul Bunel was carried out in 50 patients, yielding a positive result in two instances.

The comparison of the microbiological findings in schizophrenics with those in the controls shows considerable differences. The bacteriological study proved absolutely pathogenic flora in five cases (4 with St. aureus, and 1 with Bacterium proteus). In eight instances the antistreptolysin titer value was 250 U. In another group of eight patients no microorganisms are established except for saprophytes. In the course of virological study ECHO-virus isolated on cell cultures was found once. In the latter case the serological study was likewise positive. Antibodies to a variety of influenza strains were established through HAIR in seven patients, and against parainfluenza type 2 viruses — in one.

In the group of 100 clinically healthy individuals Streptococcus pyogenes alone was isolated in three instances, and Staphylococcus aureus — in two of the investigated cases (reliable difference compared to schizophrenics — $p < 0.001$). Antistreptolysin titer was within normal limits in 94 of the investigated cases, in four its value was 250 U rand in two patients — above 250 U ($p < 0.001$). In none of the patients were positive virus serological reactions established ($p < 0.001$).

Conclusions

1. In the course of a complex microbiologic study pathogenic flora is found in 77.06 per cent of the patients in acute stage of schizophrenia, and in 55.77 per cent — in the chronic stage. Furthermore, one is impressed by the high incidence of a variety of viral infections. The findings differ by most of the indicators from the control patients with other mental diseases, and by all the indicators — from the control, mentally intact individuals.

2. A parallelism between mental clinical picture and microbiological find is established: the heavier the course of the disease, the more frequent and massive the microbiological findings are. Most frequently, the latter are recorded during the first acute attack of schizophrenia, and in the periodic form of the recurrent attacks, showing an abatement in the chronic stage.

3. The findings mentioned above are accompanied by changes in the overall reactivity of the organism: usually subfebrile rises in temperature, speeded up erythrocyte sedimentation rate, reduction of albumins and increase in glo-

bulins, changes in the antigenic blood serum constituents with increase in immunoglobulins. In general outline, the changes referred to comply with the inflammatory (infectious) processes running an acute course, and accordingly with their chronification (V. Tzonchev et al. — 1962, Y. Todorov — 1963 etc.). This is in favour of the concept of schizophrenia as a general somatic condition in the course of which deep changes take place in many organs and systems, and in the organism as a whole, unlike the concepts of its "psychodynamic" essence or form of "existence".

4. The diversity of microbiological findings and the frequent occurrence of mixed bacteriologic, viral and bacterial-viral infections is by no means in support of the direct etiological role played by microorganisms. It is possible that in the latter case the connection and mutual effect between macro- and microorganisms are bilateral: on the one hand, the violent course of schizophrenia as a general somatic biological process facilitates the "infiltration", resp. activation of microorganisms within the macroorganisms, and on the other, they themselves facilitate the "trigger mechanism" and the rather impetuous course of the basic disease. Certainly, in some cases definite psychoses with infectious etiology could be also given due consideration, but our study does not give us sufficient reason to raise the question in terms of schizophrenia in general. At any rate, as already stressed in earlier works (V. Ivanov — 1968), the correlation virus-streptococcus in the sense of Zaleskii's idea merits special attention.

5. In this connection, the problem of our attitude to the flora of the organism as part of the complex therapeutical approach deserves particular attention, and it will be the subject of further studies.

О РОЛИ МИКРОБИОЛОГИЧЕСКИХ ФАКТОРОВ В ВОЗНИКНОВЕНИИ И ТЕЧЕНИИ ШИЗОФРЕНИИ

Л. Иванова, Г. Капрелян, Вл. Иванов, П. Стамболиев, В. Гърдевска
А. Панайотова, Хр. Димитqова, Л. Ничева, В. Русев

РЕЗЮМЕ

Проведено исследование на 213 больных шизофренией (из них 109 в острой стадии и 104 в стадии хронификации). Классическими микробиологическими методами проведено исследование секрета из горла и носа, листериновый Видаль, антистрептолизиновый титр, реакция связывания комплемента для Adeno-, ECHO, Coxsacikie, RS и Mycoplasma pneumoniae, реакция задерживания гемоаглютинации для 12 штаммов гриппа и 3 штаммов парагриппа, реакция гетерогемоаглютинации по Paul Bunel, заражение куриных эмбрионов, клеточных культур ЧЕБ и подопытных животных (новорожденных мышек) смывами и фецес.

Патогенная флора обнаружена у 77,06% больных в острой стадии шизофрении и у 55,77% — в хронической стадии. Производит впечатление частое наличие разнообразных вирусных инфекций. Эти находки достоверно различаются по большинству показателей от контрольных случаев с другими психическими заболеваниями и по всем показателям с контрольными психически здоровыми лицами.

Устанавливается параллелизм между психической картиной и микробиологическими данными: чем более бурно протекает заболевание, тем чаще и массивнее микробиологические находки. Последние чаще всего встречаются в первом остром приступе шизофрении и при периодической форме последующих приступов, уменьшаясь в хронической стадии.

Отмеченные находки сопровождаются изменениями общей реактивности организма: как правило субфебрильными повышениями температуры, ускорением реакции осаждения эритроцитов, уменьшением количества альбуминов и увеличением глобулинов, изменениями антигенов сыворотки крови с увеличением имунноглобулинов. В общих чертах эти изменения соответствуют остро протекающим воспалительным (инфекционным) процессам или их хронифицированию.

Разнообразие микробиологических находок и частая констатация смешанных бактериологических, вирусных и бактерио-вирусных инфекций не говорит в пользу прямой этиологической роли микроорганизмов. В данном случае возможно связь и воздействие между макро- и микроорганизмами двусторонняя: с одной стороны бурное развитие шизофрении как общий соматический биологический процесс облегчает «проникновение» и активи рование микроорганизмов в макроорганизме, а с другой стороны, они сам облегчают «пусковой механизм» и более бурное течение основного заболева ния.