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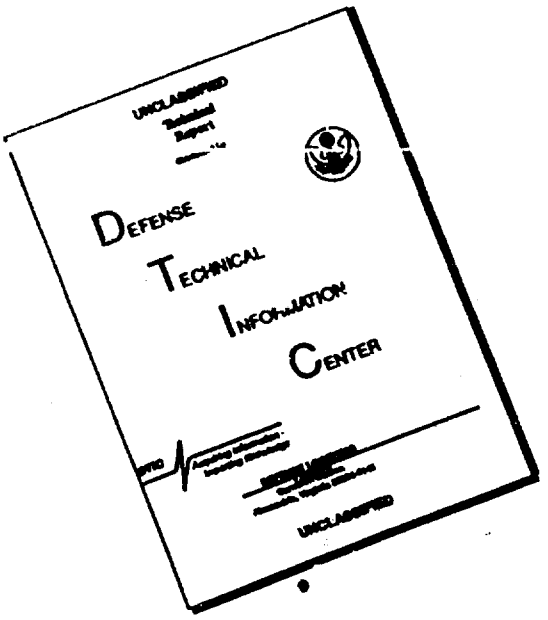

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Neuropathology and Psychiatry, 16(1), 1947: 3-17

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Pathogenesis, Clinical Symptomatology and Therapy of Japanese Encephalitis.

The particularities of the pathogenesis of Japanese Encephalitis are considered to be the paths of introduction of the virus into the human organism and its circulation within the organism.

At the present time it has been firmly established that the vectors of Japanese encephalitis are several types of mosquitoes. These mosquitoes are noted for their blood-sucking on humans in certain areas, under certain climatical-geographical situations.

A mass birth of these mosquitoes causes a concentrated attack on humans, therefore, inoculating a great number of humans with the virus in a shorttime.

The inoculation of a large quantity of this very pathogenic virus, in particular during the lowering of the resistance of the human organism, leads to a quick development of the disease, similar to the epidemics so well known in Japan.

Many years of study on the problem by my Institute, especially the studies of the last year in Manchuria, led us to establish three stages of infection of the central nervous system by this virus.

The first stage is the viral action on the endothelial walls of the capillaries and precapillaries of the brain and, it is possible, on the parenchymatous organs. While circulating and multiplying in the blood stream, the virus continuelly works on the endothelial walls of these vessels, which eventually leads to a disruption of their construction and penetrability.

The un-penetrability of the endothelial walls of the finer vessels creates that hemo-encephalitis barrier which protects the nerve elements of the brain from harmfull action. After the penetration of the endothelial walls by the virus, the blood plasma and its elements disrupt the wall further. We encounter this type action in the capillaries and precapillaries of the brain and other parenchymatous organs. This is only the first stage of the virus action on the central nervous system.

The virus, having penetrated the hemato-encephalitic barrier, enters into contact with the following mesenchymal barriers of the brain, consisting of a collection of structurally different micro- and macro-glial cells.

According to modern histology of the nervous system, the basic glial elements are astrocytes, and star-shaped cells with multiple extensions (appendages); some of which are always connected to the walls of the brain vessels. Besides this there exists another type of astrocyte, a so call protoplasmal, which are clear extensions and located near the walls of the vessels, and among nerve cells and their fibers, forming a support of the latter. Under determined conditions these astrocytes are capable of phagocytosis.

Further, among the nerve cells and their fibers, along the smaller vessels of the brain, there are other finer glios cells, so called-oligodendreglial.

Finally, a rich deposit of microglial cells, or Hortega cells, which many refer to as histiocytes, deposited in the tissue.

The sum total of the named cells receive the task of combatting the virus of a disease or toxin which penetrates the blood vessels of

the brain, and can be called the mesenchymal barrier. These cells, all different, combat any infection, including that of Japanese encephalitis. They accept the next attack after the endothelial liners are disrupted. The virus first contacts the extensions of the astrocytes, located immediately next to the capillary walls.

The virus then disrupts the glial cells by stages: tearing off and desegmentating the astrocytic extensions, infiltrating and degenerating their bodies, and also distroying other glial elements. The protoplasmatic astrocytes are like medics, cleaning the field of battle of their comrades, the astrocytic extensions and oligodendroglial elements. The microglial, or Hortega cells, after the distructive process and the field cleaning, quickly replace the destroyed elements of glial and nerve cells. The Hortega cells multiply increasingly and form gliosal scars, separating the mesenchymal waves of the healthy nerve tissues from the locale of virus destruction.

The first phase of action of the virus is the disruption of the structure of the endothelia and a lowering of its protective biological properties, which is connected with the process of exudation and transudation, then the second phase is a graduated disruption of certain elements of glia with the appearances of proliferous and partial reparative actions.

After the penetration and destruction of the second mesenchymal barrier, the virus of Japanese encephalitis reaches the immediate nerve cells and their fibers. The next stage of battle begins, as a result of which the nerve cells perish, and we encounter this phase by signs of edema and swelling of the cells and even loss and whole

segmentation of its extensions. Finally, we see the disintegration of the cell, followed by its phagocytisation and replacement by elements of the microglia.

It is understandable, in the presence of the above, that a resulting action of the great exudation and transudation will be various degrees of edema in the brain tissue. The edema increases with the further exudation, as a result of the penetration of the wall endothelia and the formation of a circulation of fluid from the basic tissue into the parenchymateus organs, in particular, into the brain.

All the enumerated processes, having reached the hypothalamus region, in which are located the centers of water and visceral balance, leads to a further increase of the edema of the brain and other parenchymateus organs, due to the disruption of the water balance.

Thus, the histopathological character of Japanese encephalitis can be directed to the following basic elements:

1. the affliction of the endothelia of the capillaries and precapillaries of the brain and parenchymateus organs, with the formation of various degrees of hemorrhaging;

2. edema of the brain;

3. various degrees of affection of certain elements of the neuroglia;

4. formation of lymphoid sleeves around the capillary and precapillary vessels, as expressed by reactive-proliferative processes;

5. certain disruption of nerve cells.

Thus, the general characteristic process with Japanese encephalitis is such: Japanese encephalitis is nothing more than a generalised hemorrhaging capillaretoxicosis with an exudational-proliferative process in the parenchym of the brain, accompanied by edema of the brain.

The localization of the pathological process in the brain, irregardless of the diffusion and generalization of the said process, should be considered with the varying degree of development of the processes in one or another section of the brain. This, evidently, is stipulated by the diversity of the angio-architecture of the brain.

In recent times it has been noted that one and the same area of brain can have varying quantities of blood vessels. For example, the region of the hypothalamus differs by having 100 times more vessels, consequently, a greater blood supply than other regions of the cortex.

It has long been established that the woundability of the subcortical ganglion is stipulated by the oddity of the vessel supply. This is why all generalization and diffusion processes with Japanese encephalitis were encountered by us in various stages or degrees.

If as a result of exacting histopathological analysis of the Japanese encephalitis, we try to establish this variance, then we would see that the intensity of the process in the cortex of the brain, certainly, is less than in that same region of the hypothalamus and central brain. More over, in the very cortex of the brain the intensity of the process is varying, in the frontal regions it is greater than in others, even though with a significant edema of the cortex of the brain they all suffer from this affection.

The intensity of the process is somewhat greater in the subcortical region. This intensity increases in the regions of the optical chiasm and particularly in the hypothalamus region. Finally, this intensity is expressed to a greater degree in the central brain, particularly on the surface of the red nucleus and black substance(substancia nigra). After this the intensity of the process significantly

decreases in the direction of the medulla oblongata; the process is expressed even less towards the spinal cord. Along with the varying degree of intensity of the process in the brain, we encounter a varying process in the internal organs, in the first place in the parenchymatous (lungs, liver, kidneys).

In these areas there is usually an excess of blood, sometimes hemorrhaging and edema. These conditions can be encountered in the suprarenal, in the mucous of the stomach and intestines, even in the cardiac muscles (in the latter case--microhemorrhaging).

The affection of the internal organs is stipulated by a direct suffering of the capillaries and precapillaries of the organ, as well as by disruption of the nerve regulator centers, in particular, the richly represented hypothalamic region.

Once more we will stress the two-fold nature of the development of edema in the brain and parenchymatous organs; as r result of the damage to the endothelia of the capillaries and precapillaries and transudation of the blood plasma into the parenchym of the brain and as a result of the disruption of the water volume and visceral centers in the hypothalamatous region. As a result there is an unequal distribution of fluid in the tissues of the organism, creating a circulation of the fluids into one direction-from the tissues into the parenchymatous organs.

B. CLINICAL SYMPTOMATOLOGY

The lenght of the incubation period of Japanese encephalitis is determined to be 5-14 days. It is difficult to establish the incubation period in connection with the constant multiplication of mosquitoes in the pre-epidemic and epidemic period. Only in certain cases, when

the individual arrives from an area where he was not affected by mosquitoes, can an exacting establishment of the incubation period be made. In last years outbreak in Manchuria the epidemiologists and parasitologists established that the infection was obtained during their stay in an area of swampland, triangled by Luba, Utoto and Tunlyao, then the infections penetrated into the Mukdena and Dairena areas, which gave an exact establishment of the varying lenght of the incubation period, stipulated by the above time elements.

The prodromal period for a majority of the patients was 2 days and was characterized by increasing headaches, general body pains, chills and loss of appetite. A Prodromal period with the above appearances was noted in 50% of all patients and in the presentoutbreak.

However, in certain cases, for so called lightning courses, those whose course is very quick, we could not establish a prodromal period.

Further development of the Japanese encephalitis is in determined stages, having specific characteristics and symptoms, stipulated to some degree by the various phases of action of the virus on the central nervous system and liquidation of the remains of the latter action.

On the basis of an accurate analysis of the clinics of Japanese encephalitis, we established the following four periods of infection:

1. initial period, related to the first 2-3 days of illness. It is characterized by a rather high temperature with general infectional and toxic symptoms. Simultaneously it is joined with general-brain symptoms with relatively poor neurological symptoms;

In the initial period there is noted, as a rule, various degrees of disruption of the occipital muscles, degrees of spontaneous or full loss of consciousness, pulse faded, variation of muscle tone in the

direction of hyperemia, especially in the extensors, variation of the function of the eye muscles and reaction of the pupils;

2. Acute period-follows the initial period for 3-4 days, or 5-6 days after the start of illness. This period is with a stable or fluctuating high temperature, during which many symptoms of affection of the brain appear, in particular, the above mentioned general brain symptoms increase, the fainting spells increase and are deepen, the # muscle tone rises, tension of the occipital muscle also, there is an interchange of the periosteal and sinew reflexes in the form of weakening or dulling, or even full absence, a tendency to perspire becomes visible, hyperemia of the face, sclera and upper chest region is clear, the coordination of eye movements becomes poorer and the pupil reaction to light is decreased, cortical, subcortical and stem symptoms. In this period the decerebration rigidness, in particular during severe cases, is clearly expressed;

3. Subacute period, or the period of decreasing sub-febrile temperatures. In this period we encounter variations of some symptoms and stabilization of others. Consciousness is clearer, but not fully returned; the pulse gradually decreases, although it is still high; the muscle tone weakens, decerebrational rigidness and tension of the occipital muscles is decreased, the periosteal and sinew reflexes are increased or even high, during this it can be noted that there is an aim towards hemiplegia. This is in conformance with the decreased muscle strenght on the corresponding half of the body and clear pathological signs--Oppenheimer and Babinski symptoms;

4. Residual period.

In passing it is worthy to remember that the pathological signs can be present in the initial period, however, they can disappear or be absent in the acute period and again appear in the sub-acute. 8.

Thus, for example, the dynamics of the pathological signs are stipulated by the various degrees of muscle tone, on the horizon of a sharply expressed action, which the pyramid system does not always recieve in the form of extensor-flexor pathological phenomena.

In this period the disruption of the coordinations is particularly sharply expressed. Tests of diadochokinesis, finger-nose and knee-heel, and an equal Romberg symptom indicate acutely disrupted coordination.

The subacute period follows the initial and acute period 7-10 days, or 12-17 days after the start of the illness. In this period early complications of Japanese encephalitis can appear; pneumonia, pyelocystitis, thrombophlebitis, bed sores, sub-membrane hemorrhaging (Translators note: could be sub-arachoid), and others.

The residual period, or period of convalescence, progresses with subfebrile or normal temperatures, with remaining symptoms of organic affection of the brain (hemiparesis, dis-coordination, general muscle weakness, cardiac phenomena, presence, in some cases, of pathological signs, decreased memory function and many other symptoms of cerebrasthenia). In some cases they progress with some psychotic stigma of types such as schizoidization, hebephrenia or maniac-depressive conditions, sometimes with delerium.

In this period the late complication are encountered, such as: pneumonia, pyelocystitis, they can progress slowly, excreting bed sores, by the acute period, forming into chroniosepsis. In this very period the disruptions of the carbohydrates volume is noted, in the form of hypoglycemia and numerous vegetative distones. This period lasts 3-6 weeks.

With Japanese encephalitis the high temperature and determined temperature curve for various periods of illness have a significant

importance. Not considering all the multiple-type temperature curves, particularly in connection with the combined residual and acute periods, all variants of temperature curve can be divided into 4 types:

1. spontaneous outbreak of a high fever, reaching 40 C with tenths, remaining here 5-6 days. This temperature curve is characteristic for more severe cases and acute forms of Japanese encephalitis, as a rule ending in death;

2. rise in temperature for 2-3 days from a subfebrile in the prodromal period to a high (40 C plus), remaining at this level for 5-7 days, with small fluctuations in 1 C levels, with a later lytic falling; this temperature curve is typical for severe, but slow forms of encephalitis; in some cases there are lethal endings, most often in 7-12 days from the start of the illness;

3. temperature which rises from the subfebrile in the prodromal period to 40 C plus and remains for 2-3 days, with a later lytic drop, some times critical. And in these cases with critical drops of the temperature there is the possibility of a lethal end, because of the cardiac weakness, but half of the patients with this curve survive; this curve is characteristic of the medium-severe course and of a relatively prolonged illness;

4. in the first 5-6 days the temperature is similar to that in type 3 above, but with later multiple, sometimes lenghty increases as a result of the joining of the sub-acute and complications periods (broncho-pneumonia, pyelocystis, excreting bed sores, etc); in some cases, especially with the accumulation of several complications, a lethal end is possible.

Let us go to the basic symptoms, their pathophysiological mechanism, localization in certain sections of the central nervous system

and their dynamics in the four basic described periods of infection with Japanese encephalitis.

As was said above, in the prodromal period we encounter several symptoms, indicating disruption of the brain membranes, such as: headaches, tensions of the occipital muscle, sometimes the Kernig and Brudzinski symptoms.

Not negating the basic meningeal substance of the said symptoms, it is, however, necessary to note that their is some dis-coordination between the tension of the occipital muscle and the lack of intensity of the Kernig and Brudzinski symptoms, and equally, it does not fall into those symptoms of the spinal fluid. Thus, these symptoms, especially that of the occipital muscle tension, are not fully meningeal. The tension of the occipital muscle-a typical phenomenon of the neck tonic reflexes, was studied by two Scotch Scientists, Magnus and Klein, and appeared as a result of any disruption, that is the disuniting of the hemispheres and sub-cortical ganglion of the brain from the medulla oblongata at the central brain level, and partially, on the level of the red nuclei.

As a result of the early appearance of edema in the brain in the sub-membrane expanses, we, therefore, encounter self-styled(odd) appearances of meningism, that is , disruption of the spinal cord membranes. But the tension of the occipital muscle is basicly part of the above mention decerebration mechanism.

As early as the prodromal period there are complaints of pain of the various parts of the body, sharp muscle pains. These pains then become acute hyperestesia in the acute, sub-acute and residual periods, which together with the hystopathological analysis indicate the affliction

of the optical chiasm or thalamus, which is one of the first to come into the process.

Quickly, however, there are other symptoms which indicate affection of the cortex of the brain; disruptions of consciousness, sleep-walking, delerium, labile aphatic disruptions; but, incertain cases, there can be weakness of the knees. With the various degrees of disruption of consciousness there are affections of the sphincter. As early as the acute state there are noted the appearances of hemiplegia. Irregardless of the sharp muscle tone, these hemiplegia soon, in the sub-acute and residual periods, form hemiparesis. All the said phenomena indicate the disruption of the frontal lobes of the brain, such as: sharply disrupted coordinations, complicated motor movements. These all indicate the affection of the lower ends of the parietal regions of the cortex of the brain.

The substance of these symptoms consists of the inability to complete simple straight movements. They are well expressed in the sub-acute and residual period, that is, after the reoccurance of consciousness.

Also clearly indicated are those symptoms of affection of the optical chiasm of the brain, that is, the occipital lobes, consisting of lack of focus ability, inability to read, inability to seek small sources of light, 'and an approaching fog', etc.

In the acute period, irregardless of the great degree of disruption of consciousness, the grasping reglex is still clearly expressed, pathognomonic for affection of the frontal lobes.

In the sub-acute and residual period the symptoms of disruption of the optical cortex system are expressed in varying degrees of decreased field of vision on white, as well as colored objects.

The temporal region of the cortex of the brain does not remain intact. Its symptoms are indicated by the sub-acute and residual periods; they are present in dizzyness, with a faultlessness vestibular apparatus, noises in the ears of varying intensity. This symptom is connected with the implication of the cochlear branch of the VIII pair of cranial nerves into the process, as well as the higher order of hearing function, that is, the temporal lobes.

In the acute and following periods, especially in the sub-acute, there is evidence of disruptionfof the function of the subcortical region, in particular, the sub-cortical lobes: facial features, skin oil, various forms of hyperkinesis in the form of little papilla movements, or choreatic-athetosis and chorec-type movements; in some cases there is a clear compulsive smile, tonic quivering without clonic components. Irregardless of such a clear semiotic of the sub-cortical regions, Japanese encephalitis does not result in post-encephalitic Parkinsonism, possibly in light of the fact that the sustansia negra is affected more, while with Ekonomo encephalitis this substance is not affected, further, the sub-cortical ganglion are affected more severly.

The symptoms of affection of the region of the III membrane or hypothalamus are many. The clearest is that of disruption of the thermo-regulator. The high temperature with patients of Japanese encephalitis and its constant lability indicate damage to the center of thermo-regulation. With this disruption there is affection of the breathing function, its regularity anddepth, with this there can be hyperemia of the face, and finally, various degrees of perspiration.

All this group of symptoms is formed by one link in the chain of thermo-regulation being disrupted through the hypothalamous region.

Even in the acute and particularly in the sub-acute period there is evidence of disruption of the various volumes, such as, albuminous, water, carbohydrate. This is indicated by the loss of weight, dryness of the bones, dehydration of the muscles, in the medical circulation of the fluids in one direction-from the various tissues to the parenchymatous organs.

This variation in the volume is indicated by the dry, crusted white tongue. The carbohydrate volume change is indicated by the presence of hypoglicemia; a sharp lowering of the quantity of sugar in the blood during the residual period was present in more than half the cases. The sugar content does not reach the minimum norm. In 50% of all patients the quantity of sugar was very small-from 45-70 o/oo.

There are degrees of distrophia in the form of ulcerous and excreting bedsores, and also in the form of processes on the stomach membrane and intestines. Thus, the clinics completely demonstrate the pathophysiological experiment of A. D. Speranski, which proved that the inclusion of any metal irritant on the hypothalamus region of experimental animals caused variations and sometimes severe distrophia.

Along with the disruption of the function of the hypothalamus region during Japanese encephalitis, it is necessary to mention the un-ordinary labilitx of the cardio-vascular system. The pulse, as a rule, even in the initial period, accelarates to 120-140 counts per minute, is tense and during sphygmography, the pulse waves are sharply increased. This type pulse wave remains through the basic and residual period, only in the agonic status does it fall. The blood pressure in the acute and sub-acute period is increased, in

the residual it can normalize or even have a tendency to fall below normal by volume indicators—maximal and minimal pressure. A period of tachycardia in the bradicardia is seldom.

The Ashner symptom is clearly established in the sub-acute and residual periods.

Analysis of the peripheric capillaries indicate a significant shrinking of them, that is, wasting of the walls of the capillaries and an acute contraction. An electrocardiograph in the sub-acute and residual period in all cases indicates disruption of the functional status of the heart, progressing as a post-infection miocardia (in 40% of the cases), or as a microhemorrhage, that is, odd microinfarct (in 20%), or a great lability of the heart muscles (30%), finally, as a disruption of the operating system of the heart (50%). It is, however, necessary to note that these conditions are abating.

The above mentioned symptoms, indicating the affection of the hypothalamus region, simultaneously explain the second principle of pathology of the internal organs to us, which augments and confirms the first principle of pathology of the internal organs (affection of the capillaries and precapillaries and varying degrees of edema). A pathological sleep or somnolence in the acute and sub-acute periods can be explained not only by the deep loss of consciousness, but, particularly with the regaining of consciousness, also by the various degrees of disruption of the region of the gray protuberance of the bottom of the III cavity, having relation to regulation of sleep and vigilance in conjunction with activity of the cortex of the brain.

Consequently, their isn't any function, existing with the hypothalamus, which in one or another degree would not be disrupted during

Japanese encephalitis. It is comforting that the disruptions of these functions, and those functions connected with the other sections of the brain, are abating, if the patient is subjected to sufficiently active treatment in all periods of illness.

The most demonstrative symptoms of affection of the central brain are external. They appear early, as cervical-tonic reflexes or occipital opisthotonus. This symptom remains the longest. The mechanism of decerebrational rigidity is expressed unusually clearly, also clearly expressed are the extensor reflexes, oddly represented by flexation of the upper extremities and extension of the lower extremities. Rotating of the head in one or the other direction or lowering it to the chest clearly indicates variation of the muscle tone in the directional muscles of the neck.

During a severe course and in the acute period, it is possible to detect symptoms of affection of the medulla oblongata; some of them can remain into the residual period. There can be paresis, and in some cases, paralysis of the facial nerves of the central area, more often of one side, sometimes of both sides, affection of the function of the cochlear branches of the ear nerve, expressed by a lower hearing ability and noises in the ears, affection of the function of the IX pair of cranial nerves in the form of loss of taste ability, presence of movement distortion of the XI pair of nerves in the form of one- or twosided paralysis of the palatine membrane, finally, affection of the function of the XII pair of nerves, expressed by a limited projection of the tongue, its angle to right or left of center and the presence of a fibrillar jerking. As a rule, in an overwhelming majority of the patients, all these affections have a pyramidal character and only in certain cases

can their action be nuclear, on the cells of the medulla oblongata.

Finally, it is necessary to point out the symptoms of the spinal cord, particularly in severe cases. These affections aremainly, if not exclusively, of the white substance of the spinal cord. These symptoms are expressed by the presence of high sinewy and periosteous reglexes in the sub-abute and residual period, when the muscle hypertonia decreases, in their odd generalization, when the knee reflex of the left is initiated, the response comes from the entire left extremity, the pelvic muscle and even the torso muscle, it leads to the presence of a spinal automatism in the form of protective reflexes to insignificant painful or cooling irritants, or to pressure on the foot, discribed as the Marie-Foix sign.

These spinal automatisms are so concise that they are typically demonstrated in physiological experiments with spinal preparations of animals. They can be evaluated as remaining phenomena of the decerebration of the brain and as disruption of the spinal-reflexer curve and conductivity aleng the pyramid system.

Also includable in the affections of the spinal cord are the disruptions of the sphincters and quick appearance of bed-sores, even though in this regard there is a double mechanism, spinal and hypothalamus for the bed sores and spinal cortex for the disruption of the sphincters.

This abundance of neurological symptoms indicates the great diffusion of the process and its acute course, and the abatement of an overwhelming majority of the symptoms- their beginning mainly as a result of discirculation mechanisms, in particular, as a result of edema of various regions of the brain.

The above described symptomatic is augmented by an odd dynamic reaction of the blood and spinal fluids, which can be recognized as specific for that disease in correlation with other discribed symptoms.

First I will point out the status of the hemato-encephalitis barrier during Japanese encephalitis.

This problem was most fully studied in this outbreak by our Dr. Kartashova. For the sub-acute, and mainly the residual period during penetrability of the hemato-encephalitic barrier, the disruption is quite significantly related to sugar and sometimes to chlorides. The variation of the PQ of sugar was in 75% of the cases, and fluctuated from 0.6 to 0.85; the coefficient of penetrability of chlorides in these patients was varied less and in fewer cases (46%). Often there was observed a simultaneous variation of the coefficient of penetrability, as with sugar, so with chlorides.

Curiously, in the acute period, of 9 examined patients, the coefficient of penetrability for sugar and chlorides was disrupted in only one, but this is still not sufficient basis to suggest that a variation of the penetrability of the hemato-encephalitic barrier in the acute period is absent. The opposite; data of analysis of the spinal fluid of the acute period indicates the presence, in all cases, of sharply positive globuline reactions during a decreased content of albumen and cytosis, which indicates the penetrability of the hemato-encephalitic barrier for the hemoglobuline albumen fractions, which in normal conditions cannot penetrate through the endothelia of the vessels. Finally, the mechanism of development of the virus action on the central nervous system with a priliminary affection of the endothelia of the vessels indicates the disruption of the penetrability of the hemato-encephalitic barrier in a very early stage of illness.

Variations of the morphological status of the blood are related to those variations discribed by Japanese authors during this form of infection, and are expressed in a majority of the cases by significant levels of leukocytosis (in the acute period from 9000 to 15000) and only in single cases is there leukopenia, evidently, connected with some kind of complicating factor. In the leukocytic formula the attention is directed to the significant increase of neutrophils (to 74-85%), a move(shift) to the left, to bacilli-type is expressed not sharply, the quantity of lymphocytes is respectively decreased, aneosinophilia in 100% of the cases is almost completly absent; monocytosis is seldom noted at the height of the illness. Normalization of the general quantity of leukocytes, as well as the leukocytic formula ordinarily terminates on the 5-6th week.

The red blood in the first days of illness differs by the presence of a moderate quantity of leukocytes and hemoglobin, a high color index and a high ESR. In the residual period in conjunction with the normalization of the hemogram, there is an exclusive lability of the blood. Therefore, these or other appearances of complications, not disclosed by the clinical symptoms, appear with the high leukocytosis, sometimes to 15000-25000, increase of the neutrophil group, in particular, of the bacilli type. During such a condition the attending doctor must try to uncover hiden symptoms of any complications. That is why the dynamic analysis of the blood of the Japanese encephalitis patients must be considered necessary.

An odd variation is also detected during analysis of the urine, and namely, decrease of the specific gravity, appearance of albumen in the urine, from a trace to a great percentage; finally, during the

development of complications in regard to the urine tract-the appearance of great quantities of leukocytes and erythrocytes in the residue of the urine. Consequently, a systematical analysis of the urine at various periods of illness is also an immediate necessity for the attending physician.

The spinal fluid in the acute period is always transparent and colorless, the albumen in the acute period, as a rule, is below normal or does not exceed the normal levels, and namely: 0.1to 0.25 o/oo. Cytosis is also slightly expressed. In half of the cases it fluctuates from 20 to 40 cells, and only in rare cases increases to 200-400. The size of the cytosis and albumen variations in the present outbreaks were within the above limits .

Globuline reactions, irregardless of the albumenous content, always are positive and in a majority of the cases sharply positive. The explanation of this is given above in connection with the penetrability of the hemato-encephalitic barrier.

Analysis of the spinal fluid in the sub-acute and residual periods gives a completely different chart; in the residual period there is an increase inalbumen of 97% of the cases, there is an increase of albumen content from 0.51 to 2 o/oo noted in 78% of the cases. All cases of hyperalbuminuria were associated with intensively expressed globuline reactions; in the residual period there was a significant increase of the formal elements of the spinal fluid (from 50-600).

Such shifts in the spinal fluid in the acute and residual periods are connected with the fact that in the acute period, as a result of the severe edema of the brain, there is a dilution of the albumen, and the absence of sufficiently expressed reparative processes does not reflect on the cytosis. In the residual period, when the reparative

processes in the brain are well represented, cytosis increases, and the increase of albumen is connected mainly with renewal of the the penetrability of the hemato-encephalitic barrier, and also, but to a lesser degree, comes about as a result of the disintegration of the albumen of the brain due to the disrupting processes.

The dynamics of variations of the eye ground in the acute and sub-acute and residual periods are interesting.

In the acute period, as a rule, in all cases there is noted a hyperemia of the papilla and in a certain percentage of cases, hemorrhaging, somewhat to a smaller degree-edema. In the sub-acute and residual periods there is noted a remaining hemorrhaging on the eye-ground , remaining edema, neuritis and even atrophia of the optic nerve. Rarely is the light- and particularly, color-perception disrupted, the field of vision is narrowed, particularly to color, various photopsia and scotoma.

All these processes on the ground of the eye and in the retina are in conjunction with the affection of the peripheric vision apparatus, as well as the vision centers, as a result of hyperemia, edema and pinpoint hemorrhaging.

Lethality during this infection is ordinarly high; it fluctuates from 40-70%. An overwhelming majority of the deaths occur in the first 7 days of illness (70% of the general number of deaths). The remaining deaths are on the 8th to 15th days, inclusively, and in certain cases the deaths occur until the 30th day; they are in conjunction with complications such as pneumonia, excreting bedsores, followed by chronic sepsis and even small local abscesses.

The survivors, even though the symptoms can return quickly, are ailing for quite some time, asthenia, physical and mental, quickly fading, and in some there is a lengthy retainment of the symptoms of idsruption of the psychiatric activity and certain neurological symptoms, connected with the lack of proper cortex function, degrees of discoordination, motor apraxia, etc.

The recovering patient of Japanese encephalitis requires follow-up observations, inregard to neurological institutes. According to those patients under our study, most of them ended up as invalids for some time.

B. THERAPY

In view of the pathogenesis displayed above, it is clear that the treatment of Japanese encephalitis must revolve from the principles of polytherapy in connection with the application of various medicamentous measures and procedures, throughout various stages of the illness. This is why principially it is impossible to allow the application of any one method of therapy, or one method of introduction of this or that medicamentous substance.

We always have in mind pathogenetic therapy and expert active utilization of so-called symptomatic therapy.

With a focus on the pathogenetic therapy of Japanese encephalitis, we must, at the present, recognize serum of convalescents or hyperimmune serum of animals. Even though the tests of the past, as well as those in the present outbreak, indicated an inadequate activity of the serotherapy during treatment of Japanese encephalitis, this negative result could be connected with the late application of it. Experimental studies as well as clinical tests indicated that the introduction of antibodies

into an organism neutralised the virus, but those disruptions which the virus caused in the nervous elements cannot be reconstructed. More so, the virus, entering the protoplasma of the nerve cells, as with any other live cells, can continue its destructive work, even in a serum medium. Thus, the neutralization of the virus takes place only in that moment when it is free to circulate thru the lympho- and blood streams, the virus, adapted, partially, to the central nervous system, evidently, cannot be neutralized.

In this, by all probability, is situated the unsuccessfulness of the serotherapy, because it, as a rule, is started on the 4th to 5th day of illness.

Taking into consideration what was said about the pathogenesis of Japanese encephalitis, in particular, about the stages of action of the virus on the central nervous system, and connecting the data of this pathogenesis with the basic clinical symptoms and with the periods of progress of Japanese encephalitis, then we can say that the serotherapy would be successfull, mainly, in the initial period, that is, in the first 2 days of illness, when the virus circulates in the blood stream, when the battle is raging between the virus and the hemato-encephalitic barrier.

In regard to the method of introduction of the serum, then again, as a result of analysis of this disease, the intravenous or intramuscular method is preferred. The intramuscular introduction insures a constant depot of antibodies, from which they enter into the blood stream, which maintains a determined level of saturation by antibodies. The intravenous path insures the neutralization of the virus circulating in the blood. The endolumbal introduction of the serum has no significance, and the sub-occipital introduction can play only an augmentating

role and, more so, cannot be highly recommended in view of the contra-indications of a sub-occipital puncture, in any respect, for half or even more of the patients with severe courses. The application of the sub-occipital puncture as a supplemental method to the intravenous and intramuscular can be placed only in those cases of medium or light severity, which, to mention, in general and without seretherapy, with properly instilled symptomatic therapy and proper care can result in full recovery.

Just as effective as the pathogenetic therapy, very likely, is osmotherapy, starting with the initial and ending with the residual period, if in the latter period there is encountered symptoms of a remaining high intra-cranial pressure.

In the number of osmotherapeutic mediums we can name there is: 40% solution of glucose (intravenous introduction), 2% solution of pyramidon (3 tablespoons per day internally) and mercuzal (subcutaneously at 3 cm3 per day in the period of maximum edema of the brain and lungs).

As a result of analysis of the pathogenesis and clinical symptomatology of Japanese encephalitis, it is necessary to note that numerous symptomatic remedies can be used as pathogenetic therapy aids and therefore, their systematic portions can sometimes have a deciding importance in respect to the favorable outcome and the prophilactics of various complications in the sub-acute and residual period.

From this we surmise the necessity of systematic portions of cardiac mediums for the support of the cardia activity, the systematic application of significant doses of camphor, in this regard as a measure of prophilactic of pneumonia. With this same regard in mind

there are are systematic applications , in the acute and sub-acute periods, of circular cupping glasses, particularly during the presence of moist hoarseness in the lungs, lobeline (subcutaneously at 1-2 cm3 per day) for the improvement of the respiratory functions. An essential aid is the maintainance of the water balance of the organism by means of subcutaneous introductions of a 5% solution of glucose and physiological solutions in ratios of 200:100 or 300:100.

We consider the systematic feeding of the patient very important. As early as the prodromal period the patients complain of loss of appetite and, as a rule, do not accept food. The initial period, as a rule, progresses with a full absence of feeding; the acute period also passes without feedings due to the disruption of all the basic types of conscious control. If we connect all these factors with the disruption of all the types of volumes during this form of illness, than we can understand the quick appearance of exhaustion, and consequently, a sharp decrease of the resistance of the organism and its protective characteristics.

This is why it is necessary to consider the application of a droplet feeding syringe, starting with the initial period, no less than twice a day, and upon return of the patient to consciousness, and increased feeding and saturation of the organism with vitamins, including B1, rations of glucose and attempts to increase appetite by any means possible, including the exclusion of unleavened bread, portions of hot food, for the increase of appitite, acids, etc.

Therapy in the residual period, in-so-far as the patient is still severly sick at this period, has an important meaning in avoiding complications and residual phenomena of Japanese encephalitis, and also in quicker restoration of the health of the patient.

Because in this period the physical and psychic astenia still remains, as well as the miscle weakness and other symptoms, indicating disruptions of the central nervous system, the lowere methabolism in the organism, then the therapy should be directed to the restoration of the methabolism and better appetite and to the stimulation of the activity of the nervous system. In the latter case we recommend no more than 4 subcutaneous injections of 1-1.5 cm3 of neostigmine ina dilution of 1:1000, with 2-3 day intervals.

As was established by studies in out institute, proserine(neostigmine) normalises the conductivity of the impulses from the neuron and neutron by means of imporving the biochemical process in the synapse of the neurons.

We also recommend a course of treatment with strychnine and continued injections of vitamin B1 as a specific vitamin for the regulation of the metabolism of the nervous system.

Again we stress the need for an increased appetite and feeding, for which we recommend, in the convalescent stage, port wine or 30% clean spirits at 100 grams twice a day before meals.

This convalescent category is contraindicative of blood transfusions. Even a droplet transfusion of blood in a small quantity will certainly lead to death. As we were surprised to find out, on one poc-r case in last years outbreak in Manchuria, then a carefully studied histopathological transfusion, after a severe affection of the walls of the endothelia, leads to a quick eruption of edema and a greater discirculation, after which the temperature rose, the neurological symptoms became acute and the patient died 10 hours after the transfusion.

This mechanism is understandable in the analysis of the pathogenesis of Japanese encephalitis.

Finally, great attention must be diverted to the care of the patient. It may mean life or death. Prophilactics for the bedsores and a constant battle with them, observation of edema of the lungs and the cardiac weakness, a systematic application of the nourishing syringe, observation of the urine sphincter, rectum, cleansing of the eyes, mouth area- all this can mean life for the patient. This is why it is necessary to have separate quarters offered such patients, insuring their proper care by a well trained staff, which can systematically and promptly manipulate the therapeutic measures.

Without a doubt it can be said that the percentage of lethal results can be regulated thru the pathogenicity of the inoculated virus, character of the systematic politherapy and degree of qualification of the hospital staff.

In closing it is necessary to stop on the question of the time of release . From the above it is plain that an early release in contraindicative. Even during a favourable course of infection and a quick abatement of the symptoms, because of the above discribed phenomena and other symptoms of disruption of internal organs, in particular, presence of hypoglycemia, death can come to these patients even though they appear healthy.

Therefore, these pathients should be retained in the hospitals no less than 1 1/2 months from the last neurological observation.

Here also we would like to mention the possibility of utilizing these recovered patients as donors for the obtaining of necessary serums. Blood can be taken no sooner than 1½ months from the start of the illness, then only if the patient is in good condition, in particular his blood and heart condition. Not more than 100 cm3 of blood should be

taken, nor should any blood be taken in the presence of remaining neurological symptoms, disruption of the eyeground, muscle weakness or dizzyness. All these should be considered contraindicative to taking of blood.

NO LITERARY REFERENCES, GRAPHS, CHARTS, ETC.