DOES AUTONOMOUS MENINGOCOCCAL MENINGITIS EXIST AND CAN IT BE INFLUENCED BY SERUM ACTING LOCALLY?

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For the first time in 1916 before the Society of Medicine of Cracow, and since 1917 in all my papers on cerebrospinal fever, I have expressed the opinion that this disease constitutes a primary ventriculitis, the actual lesions of the meninges being only a secondary phenomenon. I have endeavoured to supply the necessary proofs in support of this view in my sixth communication (1922, 1924) and, in English, in an article published last year in *The Lancet*.

I may now say that this new conception has been entirely adopted by C. Dopter, the well-known authority on the subject. It has to be emphasized, however, that it is not under the influence of my proofs that this author changed his former opinion. These were quite unknown to him when he wrote his recent paper, as he quotes only my third communication (1919). Thus his conviction is based principally upon his own histological studies, by which, in fulminating cases, immediately after the onset of the disease, an acute inflammation of the choroid plexuses of the cerebral ventricles has been demonstrated.

But even though we are now in complete agreement with Dopter and some other French authors (e.g., Cestan and Riser) as regards the principal problem, there still remain certain questions, less essential, yet of considerable importance for the practice of serotherapy, concerning which, I am afraid, a divergence of opinion remains; these differences still claim special studies for their definite solution.

Thus we may ask the question whether it is possible that, in a subarachnoid space blocked by adhesions, meningitis exists independently of the infectious process in the ventricles and requires a serum treatment entirely on its own account.

In dealing with this problem, we must first understand clearly what is the exact meaning of "cloisonnement," blockage, or obstruction of certain parts of the ventriculo-subarachnoid system.

Now the French authors suppose that, in some cases, the purulent exudate accumulated in the basal cisternæ—sometimes also the exudate found around the spinal cord—may, in consequence of resorption,

form a thick and resistant mass. The process of organization therein causes the formation of fibrous strands which eventually partition off the subarachnoid space into numerous sacs. These, closed on all sides, thus become independent of each other and can stem or even interrupt the free circulation of the cerebrospinal fluid. So the lesions develop in each of them independently and assume different aspects. The same fibrous strands or, in some cases, purulent flakes, in the form of a " stopper " or narrowings due to ependymal swelling and scarring, may also—always in the opinion of the French authors—cause an obstruction of the foramina of Magendie and Luschka, and thus a general blockage of the ventricles ; in other cases, an obstruction of the Sylvian aqueduct or of either foramen of Monro may occur.

To judge from my own observations, these various blockages are more than problematical. There exists one unquestionable blockage, however, also admitted by the French authors ; it is that which develops in the neighbourhood of the foramen magnum. In my opinion, however, the view that has hitherto been held as regards the process of formation of this obstruction is not correct. I believe this blockage arises in consequence of the medulla oblongata and the adjacent parts of the cerebellum becoming wedged into the foramen magnum as a result of the inflammatory cerebral œdema. The subarachnoid spaces therein become more and more narrowed and may eventually, in some cases, be completely closed and occluded by the formation of adhesions. Apart from the obliteration of the subarachnoid space—to be ascertained by the introduction of a probe under the arachnoid—external adhesions between the arachnoid and the dura mater are generally still found.

We next inquire what are the effects of this blockage (which in some cases is undoubtedly complete) upon the infectious and inflammatory processes of the spinal subarachnoid space, which has thus lost its connection with the ventricles. To ascertain this is most important, as we are thus able to form a general rule and to avail ourselves of it as a standard in order to decide whether other blockages are or are not complete.

I have at hand only two cases (62* and 94*)* in which this blockage actually developed under my observation to become finally complete. Neither case was treated with serum at that stage. It is important to bear this in mind, as hitherto certain authors (e.g., Dopter) have been inclined to refer certain symptoms, e.g., xanthochromia and high albumin content in the spinal fluid, to the presence of serum injected but not absorbed, and the retrogression of the infection and suppuration to its therapeutic action. In both cases the ventricles continued to be

* The observations marked with asterisked numbers are, in my papers, illustrated with synoptical cuts, representing all their essential clinical symptoms as well as the results of investigations.

abundantly infected, and in one of them the patient, a bottle-fed, rickety, dyspeptic and atrophic baby, was in a most precarious condition, but nevertheless exhibited a feeble general immunity; the child's own serum gave, with autogenous culture, a complement-fixation reaction in a dilution of 1 : 10.

We may define the effects of complete blockage as follows :—

1. Complete disappearance of the meningococci from the spinal fluid.
2. Almost complete disappearance of the polynuclears, i.e., pus cells.
3. In addition to this, symptoms of stasis of the spinal fluid, on which Foix, and subsequently Mestrezat, have particularly insisted, viz., very marked xanthochromia, very high albumin content and albumin index, abundant globulins, massive coagulation, low pressure, rapidly diminishing during evacuation of the fluid, and the impossibility of obtaining on puncture greater amounts of the latter. These symptoms of stasis always occur, but they cannot be regarded as reliable signs of complete blockage, for they may precede it by several days. Further, sugar is absent from the spinal fluid, which is probably owing to the infection continuing to evolve in the ventricles, and this would possibly constitute a differentiation from the condition of meningeal intolerance towards serum.

Let us now apply the above definitions as a standard for those cases in which their reporters have thought they were dealing with a complete blockage; we shall soon be persuaded that the vast majority of these cases did not present the above syndrome. Consequently there was no question of blockage at all, or at least no complete blockage. We find, for instance, mention of the presence of polynucleosis (purulence). In other cases, it is true, authors have noted the absence of cocci and suppuration, but they emphasized the fact that " together with the regressive condition of meningeal inflammation, the spinal fluid was clear, limpid or slightly opalescent, still slightly hyperalbuminous, or even having its albumin content fallen again to the normal state " (Dopter). In short, the fluid exhibited no signs of stasis, which, in my opinion, is completely incompatible with the idea of true blockage.

Some might consider our standard to be false, though personally I do not suppose so. Nevertheless, nothing prevents us from submitting it, in the future, to suitable tests. Meanwhile, let us see the reasons that have induced writers on the subject to assume the presence of a complete blockage.

In their opinion, the most convincing evidence has consisted in the differences in appearance between the fluids yielded on the one hand by the partitioned sac, on the other by the ventricles or the spinal space. These differences, however, prove nothing at all. They may be determined by varying local conditions (production and resorption

of the fluid, its current and up-and-down motion, relative stasis). In my former papers I have, I think, sufficiently brought out the profound differences often existing between the ventricular and spinal fluids without their communication being seriously affected.

Marfan has endeavoured to supply another proof. In his case autopsy showed the existence of four infectious foci isolated from each other by obliteration of the Sylvian aqueduct, obstruction of the foramina of Magendie and Luschka, and by adhesions in the region of the foramen magnum. Now the author injected, after death but before autopsy, a solution of methylene-blue into the ventricle. The dyestuff localized itself strictly in the injected ventricle, as a lumbar puncture performed half an hour afterwards showed that the blue stain had not diffused at all into the spinal canal; also at autopsy the surface of the brain had kept its normal colouring.

This experiment does not appear to me to be at all convincing. (1) After death the current of the fluid as well as its up-and-down motion, i.e., all the movements that in life contribute to spread the dyestuff, are stopped. (2) Even in the living subject methylene-blue is not suitable for such tests. Indeed, in one case (related in my sixth communication) in which there were very obvious symptoms of impaired communication, methylene-blue, injected into the ventricles three times during life, produced no blue coloration in the spinal fluid. Nevertheless, the communication was not completely stopped, as was proved by (1) the passage of serum injected into the ventricles; (2) the penetration of the cocci of a fresh ventricular streptococcal infection; and (3) the slightly blue coloration of the fresh pus deposited in the region of the cauda equina.

But why did methylene-blue not appear in the spinal fluid? The explanation is very simple. The spinal fluid was very xanthochromic, and contained 5 per cent. of albumin, this content thus approaching that of the serum plasma. There was no question of injected serum, for the dosage of serum with anti-horse precipitating serum showed on the twenty-fourth, thirtieth and thirty-first days of the illness only 3·0, 0·3 and 0·1 per cent. of horse serum, the albumin content remaining the same. Thus we cannot but conclude that the fluid was charged with the blood plasma of the patient himself in consequence of stasis, and contained about 60 per cent of it.

Now, in such hyperalbuminous fluids, methylene-blue seems to be very quickly reduced to achromatic combinations. To convince oneself of this it is sufficient merely to inject intravenously into a rabbit pure methylene-blue in a dose of from 4 to 5 c.c. of a 1 per cent. solution per kilogram of body weight. This corresponds to a proportion of from 5·2 to 6·5 c.c. of the staining solution to 100 c.c. of its serum, and would give the fluid a strong blue coloration. Yet the serum obtained from

the blood withdrawn five minutes after injection is scarcely stained a slight blue, and the serum of the blood withdrawn half an hour after injection is generally only yellow. Yet the urine secreted hours afterwards is blue.

The proper substance to employ in order to investigate these circumstances of maintained, impaired or interrupted communication is antimeningococcal serum. In its character as horse serum it may be determined everywhere with sufficient exactitude by using a specific precipitating rabbit serum. Thus we are never justified in assuming a complete blockage, unless we prove that serum injected into the ventricles does not penetrate into the blocked space.

To conclude the discussion of this question there remains to be emphasized the fact that each complete blockage constitutes a durable and irreducible lesion which, even after the disappearance of the specific infectious process, inevitably leads to severe disturbance, almost without exception incompatible with survival. Consequently, when reading observations where the authors assume a blockage and where nevertheless they affirm they have obtained perfect recoveries, the suspicion becomes legitimate that those blockages were only partial, relative, and thus reducible.

Lastly, let us recollect that Ramond was inclined to assume that a partition, though it brought about an anatomical blockage, sometimes allowed the meningococci of the ventricles to filter through microscopic fissures and infect subarachnoid spaces. According to his expression, then, the question is whether " infecting ependymitis " contributes to maintain specific meningeal infection. His opinion, we see, approaches mine very closely.

The same cause that produces blockage in the region of the foramen magnum, the cerebral œdema—and not the partitioning in the basilar region—leads also to progressive narrowing, and in some cases to obliteration of the cerebral sulci. Very exceptionally, in the course of the evolution of this obliteration, a certain part of the subarachnoid space may, without being obliterated, lose its communication with the ventricles. This seems to have occurred in one of my cases (No. 149*), for the fluid evacuated on the twenty-fifth day of the illness, through a vertex puncture to a depth of 8 to 15 mm.—also in this case before any serum injection—showed all the essential characters of complete blockage: marked xanthochromia, high albumin content, globulin reaction strongly positive, pressure rapidly diminishing to zero during evacuation, absence of meningococci in spite of abundant ventricular infection, absence of sugar. Nevertheless, polynucleosis was predominant (94·2 per cent.), probably because the blockage was still of recent date or, in spite of all, incomplete.

The process of disappearance of the meningococci is in all these

cases quite clear. In the latter observation the patient's serum showed, according to the complement-fixation reaction, the therapeutic value of 63. The albumin content of the fluid in the blocked sac was 3·2 per cent., which would correspond to a plasma content of 38 per cent. and confer a value of 24 on the fluid. As a fact the fluid, examined by means of the complement-fixation reaction, exhibited almost this value (6·3+, 20±). The same situation was also found in case 94* in the blocked spinal theca : value of patient's serum, 10 ; albumin content of the spinal fluid, 6·25 per cent., which would correspond to a plasma content of 75 per cent. and give the fluid a value of 7·5. The existence of meningococci in the blocked spaces thus becomes impossible owing to general immunization, even if the latter be quite insignificant, because this immunity must comprise a space containing in reality blood plasma which is only slightly diluted.

Complete blockage affecting ventricular orifices or the Sylvian aqueduct seems, in my opinion, not to be proved, though, particularly as regards the former, considered fairly frequent by French authors (Dopter, Marfan). At autopsy we sometimes see, it is true, certain lesions of these orifices which might impair the communication without completely interrupting it, but these lesions seem to me rather secondary than primary in their relation to the feeble motion of the fluid. Indeed, in these advanced cases we are compelled to assume that the interchange of the fluids between the ventricular and the subarachnoid spaces is exceedingly reduced, the extremely slow disparition of injected serum being the best proof of this. For example, in case 148*, which was that of an infant in its first year, admitted in a very advanced period of the disease, with very marked hydrocephalus, we saw that serum injected through the lumbar puncture penetrated quite well into the ventricles. This proved that the communication between the ventricles and the spinal space was perfectly maintained. But observing, after the last injection, the disappearance of the serum, we ascertained that a reduction to a tenth was here accomplished in about a week. Now we know that in ordinary cases such a reduction to a tenth occurs generally in about a day and, in cases showing considerably narrowed ventricles, it may occur in two hours or even in an hour. The knowledge of these differences is very important, the disappearance of serum constituting the only rational indication for repetition of the injections. For our argument it is to be borne in mind that notwithstanding the maintained communication, serum disappeared, in the above case, extremely slowly. Consequently the interchange of the fluid between the ventricles and the subarachnoid space was undoubtedly extremely reduced. It must appear quite obvious that, under these circumstances, narrowings of the ventricular orifices may very easily occur as a secondary lesion, especially if the infection is not yet overcome.

Let us now turn to the question of treatment.

From all I have said of the characters of the complete blockage, it is quite plain that a blocked subarachnoid space can claim no treatment with serum on its own account. In fact, as we have seen, the infectious process and suppuration disappear as soon as complete blockage is established.

If the blockage is incomplete, and in spite of this, treatment of the ventricles alone will be sufficient, because the suppression of the ventricular infection will also instantly make the process in the partially blocked sac disappear, the latter process constituting only a sequel of the ventricular infection. In addition to this, the serum present in the ventricles will in such cases always penetrate into the sac just as do the meningococci. Only it may be found—contrary to what is seen in ordinary cases—that the serum will here be in a somewhat lower concentration than in the ventricles. For instance, in the above-mentioned observation 10 per cent. of serum was found in the ventricular fluid evacuated seven hours after intraventricular injection of 11 c.c. of serum, while the spinal fluid contained only 3 per cent.

Moreover, to justify the local treatment of a subarachnoid space, whether obstructed or not, it should be proved that serum acting therein, but without exerting simultaneously any action upon the ventricles, can really produce a therapeutic effect.

Such an action limited to the subarachnoid space can only be observed under quite special circumstances, for generally the serum present in the subarachnoid space penetrates easily (cases **143***, **144***, **148***), or at least fairly well (cases **146***, **147***, **149***), into the ventricles.

But when, in consequence of cerebral œdema, the ventricles are considerably narrowed, the serum injected through the lumbar puncture may well spread throughout the subarachnoid space, without, however, reaching into the ventricles in the concentration required for therapeutic action (**145***, **151***). In these cases even bilateral injections through the temporal puncture often do not change the situation essentially. Indeed, the current of the fluid is very rapid in the narrowed ventricles, quickly rinsing the serum out and carrying it into the subarachnoid space, where it may be found in a fairly high concentration, sufficient for therapeutic action (**141***, eighteenth day of illness). We observe the paradox of the situation: the serum has been injected into the ventricles and is, several hours after injection, practically absent therefrom, while it is present in the subarachnoid space. Moreover, in addition to this, in cases exhibiting an inflammatory hydrocephalus, we have also had an opportunity of noting on occasion that serum injected intraspinally does not penetrate sufficiently into the ventricles (**146***, **152***).

Now in none of these cases do we ever see any influence of the serum, not only on the ventricular infection, but even upon the infectious and inflammatory condition of the spinal space itself, in spite of the serum being found there in a concentration sufficient for therapeutic action. Moreover, in my opinion, it is rather difficult to conceive how this influence can make itself felt so long as the spinal space continues incessantly to receive from the ventricles a fluid sometimes abounding in meningococci. Thus, these observations and the reflections arising from them make it quite evident that the presence of serum in the subarachnoid space is of no therapeutic value whatsoever, even for this space itself, and that only the serum present in the ventricles exercises a decisive action upon ventricular as well as upon subarachnoid infection.

The negative effect of the local treatment of the meningeal process constitutes one of the most convincing proofs in favour of the opinion that meningeal infection is never independent and autonomous, but always closely subordinate to the ventricular infection.

If I add further that—contrary to many authors (Dopter, for instance, speaks of absolute necessity)—I have never been compelled to apply, in addition to specific local treatment of the ventricles, any general serotherapy (i.e., intravenous, intramuscular or subcutaneous injections); that in many cases the indication for this therapy seems to me to have been laid down by observers in ignorance of what is going on in the ventricles; moreover, that this administration of serum appears quite superfluous on account of the fact that the serum injected into the ventriculo-subarachnoid system passes very rapidly into the general circulation, we shall easily realize that my therapeutic indication will be very simple in principle:

Disregarding subarachnoid or general infection, let us bring about a sufficiently intense serum action in the ventricles, and maintain it uninterruptedly for several days, until the stage of complete disappearance of meningococci, verified by examination of the ventricular fluid, is reached.

As regards the results that can be obtained if we proceed according to these principles, I cannot here enlarge upon this point, and am obliged to refer to what I said at a meeting of the Pediatric Section of the Royal Society of Medicine. It has only to be emphasized that, in 80 per cent. of cases, a sufficiently intense serum action in the ventricles can be realized even by intraspinal injections. Thus in only 20 per cent. of cases does intraventricular application become indispensable; further, that the supplementary reduction of mortality of cerebrospinal fever, produced by the latter method, is, according to my observations, 16 per cent. in patients over two years of age, and 10 per cent. in infants in their first year.

BIBLIOGRAPHY.

[1] CESTAN and RISER, *Gaz. des hôp.*, 1924, No. 81.
[2] DOPTER, C., *L'Infection méningococcique*, Paris, 1921.
[3] DOPTER, C., *Congrès français de méd.*, Paris, 1923.
[4] DOPTER, C., *Paris médical*, June 7, 1924.
[5] LEWKOWICZ, K., (Observations 15–62*), *Przeglad lekarski*, 1917, and *Wien. klin. Woch.*, 1918, No. 21.
[6] LEWKOWICZ, K., (Observations 85–114), *Przeglad lekarski*, 1920, and *Arch. de méd. des enfants*, 1921, Nos. 6, 7.
[7] LEWKOWICZ, K., (Observations 116–140), *Rozprawy Akademji Nauk Lekarskich*, 1922, and *Arch. de méd. des enfants*, 1924, Nos. 3 and 4.
[8] LEWKOWICZ, K., (Observations 141*–142*), *Polska Gaz. lek.*, 1922, and *Monats. f. Kinderheilk.*, 1923, xxvi.
[9] LEWKOWICZ, K., (Observations 143*–147*), *Polska Gaz. lek.*, 1922, and *Monats. f. Kinderheilk.*, 1923, xxvi.
[10] LEWKOWICZ, K., *The Lancet*, September 6, 1924.
[11] LEWKOWICZ, K., *Pediatric Section of the Royal Society of Medicine*, London, May 22, 1925.
[12] MESTREZAT, W., *Revue neurol.*, 1923, No. 6.
[13] MARFAN, *Bulletin médical*, February 5, 1916.
[14] RAMOND, *Soc. méd. des hôp.*, May 25, 1916.