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HEMORRHAGIC GLOMERULONEPHRITIS AFTER SUBCUTANEOUS INJECTION OF POLYVALENT ANTIDYSENTERY VACCINE

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(Contemporary Medicine)

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The etiology of glomerulonephritis in man still remains unclear despite successful experimental studies in this direction. We know that experimental glomerulonephritis resembling, more or less, human glomerulonephritis could be provoked with the help of heterogenous proteins or microbe agents mainly with the help of three different methods (9):

1. Through intravenous injection of the so-called nephrotoxic serum which is obtained from another animal species, immunized in advance with an extract from the kidney tissue of the experimental species.

2. Through intravenous injection of single or multiple large doses of normal serum proteins from another animal species.

3. Through intravenous or intraperitoneal injection of certain bacteria and bacterial products, most frequently in combination with a nephrotoxic or other serum.

The largest and most successful experiments were those involving various types of streptococcus. It was determined that that glomerulonephritis is caused not by the streptococcus themselves but from the products of their lysation. It is interesting to note that no model of experimental glomerulonephritis following subcutaneuous injection of microbe agents has been described. Only C. Wood and R. White (9) have reported experimental glomerulonephritis in white mice following the subcutaneuous injection of a culture of Proteus mirabilis, killed through heating.

We are unaware as to the extent to which such proteins and microbe agents play a role in the etiology of glomerulonephritis in man, and how. Various speculative analogies and hypotheses have been drawn on the basis of

experimental data. Therefore cases of glomerulonephritis in man in which the etiological role of a given agent could be clearly determined are of great theoretical and practical interest. We were able to observe this in an accident involving a group of children in whom a "model of experimental glomerulonephritis" was developed following a mistaken subcutanueous injection of polyvalent dysentery vaccine.

On 28 April 1955 16 students from a settlement in the N. Okoliya, aged 12 to 14, during their immunization against typhoid fever, were mistakenly vaccinated subcutanueously, the third time with 1 cubic centimeter of polyvalent dysentery vaccine instead of typhoid vaccine. The error was due to an accidental mix-up in the vaccine bottles. The dysentery vaccine (series 60, AK No. 318) was to be absorbed per os. It had been prepared out of Flexner, Zohne and Grigoriev-Shiga bacilli, killed through heat. One cubic centimeter contained ten billion embryos. The same day, a strong swelling and reddening of the skin at the spot where the injection had been administered showed up. Some of the children suffered from general fatigue, headache and, later, vomiting. They did not develop diarrhea. On the third day all children entered the hospital for treatment. The tests revealed that their urine contained albumin, grandulated cylinders, erythrocites and cells from the epithelium of the kidneys; their blood showed an increased content of urea from 50 to 90 milligrams %.

Five of the children were affected more severely. They included Yu. R. Sh., 14 years of age, who died and on whom we conducted a pathologo-anatomical study. On the sixth day he went into tonic-clonic spasms; his neck became rigid and he lost consciousness. The spasms were repeated several times during the next few days. Laboratory tests revealed the following: urea in the blood--91.2 milligrams %, leucocytes--12,500; the bone marrow liquid flowed in puncturing under higher pressure; it contained 166 milligrams albumin and 275/3 cells; the urine had albumin, 8 to 10 erythrocites per field, granulated cylinders and kidney epithelium. The patient was treated with chloralhydrate, luminal, calcium bromate, glucose, cortigen, vitamin C, penicillin and streptomycin. The condition of the child rapidly worsened, the coma state intensified and the child died on the eighth day following the injection of the dysentery vaccine.

The autopsy was performed 20 hours after the patient died. The skin above the armpit of the right hand, where the injection with dysentery vaccine had been administered, was found to be red and quite swollen. The underlying soft tissue and muscles were juicy, breakable and imbued with abundant turbid liquid. Histologically we could see among the subcutaneous fatty tissue and muscles centers of necrosis, swelling, hemorrhages and layers of serous-purulent exudation.

In the internal organs, the greatest changes were noticed in the kidneys. They were slightly swollen. Their capsule was easily removable. The surface was smooth. It showed many small red spots resembling flea bites on the skin. The kidney tissue was juicy. The cortex showed above the level

of the pyramids. It showed a scattering of many blood spots. The pyramids were pale with unclear radiation. The basins and the bladder were empty. Their mucus membrane was smooth, shiny and whitish. It showed single point-like hemorrhages.

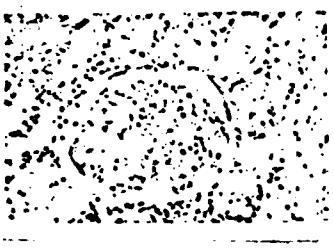

Figure 1

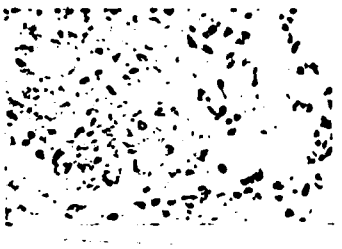

Figure 2

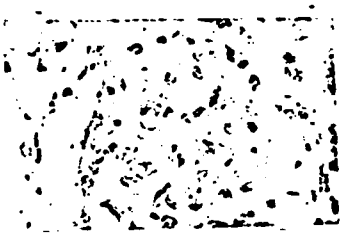

Figure 3

Figure 4

The histological study of the kidneys revealed rather severe damages to the entire functional apparatus. The capillary stitches [stitches] of the glomerules were almost diffusely clotted by homogenous masses of albumin and erythrocites (Figures 1, 2, 3). In some of the glomerules the structure had been entirely erased as a result of such a severe infarct of the capillary network. The walls of the capillaries were imbued with albumin matter. The basilar membranes could not be traced. The endothelic and epithelic cells were swollen and juicy. Some of them displayed degenerative symptoms. Exudate had accumulated around the thus changed capillary stitches, containing erythrocites and single leucocites (Figure 4). A small amount of this exudate was found in the capsular space as well as in the lumens of the canals, forming cellular cylinders. The parietal sheath of the capsule of the glomerules was less affected by the process. The epithelium cells which covered it were slightly swollen. Here and there some of them had fallen in the capsule area.

The epithelium of the first and second grade loops as well as the Henle loops was almost totally necrotized. The epithelium cells had blended in homogenous pale pink nucleus-less masses which entirely blocked the lumen of the canals (Figure 5). The interstitium around them included rich inflamed

were not affected. It is noteworthy that the process was identical in the mucous membranes of the respiratory ways, the stomach and the intestines.

Swelling, hyperdmia and single diapedic hemorrhages were found in the lungs and the brain and, to a lesser degree, in the miocard and the liver. The parenchymous elements of these organs displayed moderate dystrophic changes.

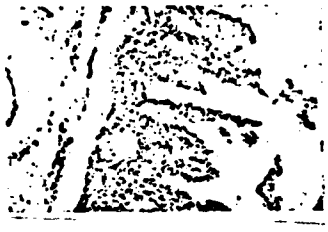

Figure 9

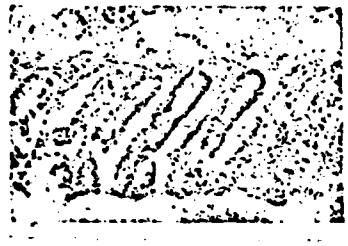

Figure 10

The spleen was slightly swollen with a pensed capsule. It was filled with a great deal of blood. The reticular and endothelic cells as well as the lymphatic foliculae displayed no particular changes. The lymphatic ganglia and the bone marrow also displayed hyperemia and a swelling with no particular reaction on the part of the parechyma and the reticulo-endothelic elements.

The endocrinic glands had no particular changes.

The bacteriological study of tissue taken from the place of the injection, the spleen, the gall bladder, the lymphatic ganglions and the kidneys did not reveal any dysenteric or other morbid microorganisms. No antidysenteric antibodies were found in the blood.

On the basis of these changes in the organs the following pathologo-anatomical diagnosis was made: serous-purulent-hemorrhagic inflammation of the skin and the subcutaneous tissue of the brachium of the right hand following the injection of polyvalent dysentery vaccine on that spot. Acute diffused hemorrhagic glomerulonephritis. Serous swelling and many dot-like hemorrhages on the serous tissue and the mucous membranes. Catarrhic tracheobronchitis and gastroenterocollitis. Swelling of the lungs and the brain. Parenchymatosic dystrophy of the myocard and the liver. Hypermia of the pulp of the spleen.

The clear link which exists between the dysentery vaccine and the disease as well as the above-described pathologo-anatomical picture leave no room for a differential diagnosis involving other similar diseases. We could question whether it is not a contamination with the virus of the

hemorrhagic fever, more especially its far-Eastern variety known as hemorrhagic nephroso-nephritis. This is not confirmed by the pathologo-anatomical picture. Hemorrhagic nephroso-nephritis has characteristic hemorrhages in the pyramids of the kidneys and the front end of the pituitary gland, which are missing in our case. Here the hemorrhages affect the glomerules and the interstitium of the kidney shell. Here, as in the case of the children who remained alive it was clear that the damages to the kidneys and the other organs had been caused by the dysentery toxines contained in the vaccine which was erroneously administered parenterically, in such a high amount. We have been unable to find any other description of such a case.

This unfortunate event raises some interesting questions on the pathogenesis of bacillar dysentery as well as glomerulonephritis.

We know that the dysentery toxines stemming from the multiplication of the bacilli in the intestines are easily resorbed in the blood and thus create the general intoxication manifestations of the disease. This has been confirmed experimentally as well. Dysentery endotoxins administered to experimental animals, marked with radioactive isotopes, shortly afterwards are manifested in the blood (6). This is the basis for the widespread hypothesis according to which damages to the mucous membrane of the big intestines in dysentery are due to the dysentery toxines which pass through the membrane like other toxic products having been initially resorbed by the blood (3). The thus damaged mucous membrane creates conditions for the further development of the dysentery and other microorganisms of the intestinal flora. It is precisely thus that the characteristic localization of the damage in the big intestines is explained.

Many serious objections have been made to this hypothesis (2). Our own observation is equally unfavorable. We have no grounds to accept, on the basis of the picture described above, that the dysentery toxins which were introduced parenterically in the body with the vaccine have been radiated through the mucous membrane of the big intestines. The inflammatory and circulation changes here were not of an isolated nature as in the case of dysentery. They were almost identical to the changes in the mucous membrane of the other parts of the gastrointestinal tract and the respiratory ways. Furthermore, they were far lighter than the damages done to the kidneys. This confirms the fact that the toxines came through the kidney filter as a result of which it was so severely damaged. Of late V. L. Troytski and M. A. Tumanova (7) studied, with the help of marked dysentery antigenes their mechanism of separation from the body. They determined that the antigenes introduced through different ways (per os, subcutaneously and intravenously) always penetrate into the blood and come out with urine. The parenterically introduced antigenes have not been found in the feces. This does not confirm the hypothesis of their passage through the mucous membrane of the big intestines. On the basis of all this we may consider in our case that the damages done to the mucous membrane of the big intestines as well as the other organs are due not to the fact that dysentery toxines passed through them but to circulatory disturbances which occured as a result of the damage done to the vessels by the toxines. Undoubtedly, a certain role was

played by the toxic products retained in the body as a result of the kidney insufficiency.

Many authors describe kidney damages in dysentery similar to those noticed in our case but only in a lighter form. M. A. Skvortsov reported such cases in 8.7% of 1,832 autopsies of children died from dysentery and L. O. Vishnevetska, with more careful microscopic studies, found them in up to 20% of the cases. It is considered that the kidney damages are due to the disturbed exchange of matter due to the damaged mucous membrane of the big intestines through which go many refuse toxic products. Our observation does not confirm this explanation. The kidney damages, clinically and pathologo-anatomically, were more severe than those of the intestines and quicker. This leads us to believe that in this case they do not depend on any damage to the secretive function of the big intestines but to the direct influence of the dysentery toxines in their secretion with the urine.

The dysentery toxines manifest a clear vasotropic harmful effect. This is confirmed by the above-described generalized circulatory disturbances and hemorrhages in the organs. These damages were most severe in the capillaries of the kidney glomerules since it was there that the highest accumulation of dysentery toxines in their secretion occurred. The dystrophic changes of the parenchyma of the organs and, more especially, the tubular machinery of the kidneys could be explained as a consequence of the ischemia resulting from the vascular damage. The inflammatory infiltrate in the interstitium of the crust is a reaction to the irritation created by the necrotized epythelium of the canal.

It would be pertinent to ask whether the vasotropic and, particularly, the nephrotopic harmful effect of the dysentery toxines is not the manifestation of an imuno-allergic reaction which is considered so important in the pathogensis of the glomerulonephritis or dysentery. In our case we have no grounds to assume the development of such a reaction. The kidney damages occur almost with no interval whatsoever following the administration of the dysentery vaccine. The serological tests did not show any antidysentery antibodies. There are equally no grounds for paying any particular attention to the sensibilization of the body created by the previous two injections of typhoid fever vaccine. Obviously the glomerular and other vascular damages are due to the immediate primary harmful effect of the dysentery toxines. This fact is quite interesting. It indicates that the development of glomerulonephritis in man must not be always preceded by a sensibilization of the body against the effect of a given agent. Damages to the glomerules may be the result of an immunal-allergic reaction or the primary direct impact of the toxic agent. Perhaps this is the reason for the two different forms of human glomerulonephritis as described by the British theory of Ellis.

Our observation is interesting also because it is a "model of experimental glomerulonephritis" created through the subcutaneous injection of bacterial products. As we already pointed out all the described models of experimental glomerulonephritis develop in the case of intravenous or

intraperitoneal injection of microbe agents. Only Wood and White have been able to reproduce glomerulonephritis in white mice with subcutaneous injection of the culture of Proteus mirabilis, killed through heat. We are also conducting experiments in transferring the model observed by us to an animal, to study it in greater detail. It appears that most of the laboratory animals do not react with such tissue changes in the kidneys or other organs as described in our case. Actually, this is known from the pathology of experimental dysentery.

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