

Neonatal pseudomonas septicemia

(Histopathologic observations on four cases)

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Ever since the pioneer papers from the end of the last century and the beginning of the present, just after the discrimination of this type of bacteria (*Bacterium pyocyaneum* — Gessard-Flugge, 1882), the pathogenicity of the *Pseudomonas aeruginosa* is well-known in children, old persons and chronic ill patients has been accentuated (1,2,3,4,5,6,7,8,9,10,11). Its preference for debilitated organisms, children, old persons and chronic ill patients has been accentuated since the earliest observations. The newborn, mainly the premature, is more susceptible to this bacteria, and epidemics of *Pseudomonas* infection in nurseries have been related (4,5,12,13,14,15,16,17).

The analysis of the published cases shows the severity of this type of infection, by the rapidity of evolution, commonly fatal, with necrotic cutaneous and visceral lesions, caused by the septicemic process.

The histopathologic study of four cases, prematures who died during an epidemic in the nursery of the "Maternidade Clovis Corrêa da Costa" of the "Instituto Fernandes Figueira" — Rio de Janeiro, gave us the chance to study the characteristic lesions of *Pseudomonas* septicemia, allied to the presence of kernicterus in three cases, a fact we did not see reported in the revised bibliography.

CASE REPORTS

Case I

History — N. B. S. (Hosp. 371/62), negro, female, born of normal delivery (1555 g; 43 cm; Apgar 9). Immediately after birth presented dyspnoea and disseminated pulmonary rales, symptomatology which disappeared 24 hours later. No abnormalities on the following days. On the fourth day she became jaundiced, irritable, hypertonic with flexion of the limbs and scleredema; the respiration was irregular with disseminated pulmonary rales. The weight decreased gradually; no hyperthermia. The symptomatology remained the same and she died on the sixth day of life.

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Necropsy findings — macroscopic examination reveals a normal premature, exhibiting mild jaundice, hard edema of the legs and palpebral edema; protruded abdomen, liver palpable 2 cm below the costal margin. Head and brain — no abnormalities. *Thoraco-abdominal cavity* — presence of little bloody fluid in the right pleural cavity; lungs of black-red colour, uniformly hardened consistency, non crepitant, exhibiting a few light coloured areas; the cut surface shows uniform aspect (W.: 37g; N.: 27g). Esophagus, stomach, small and large intestines exhibiting marked congestions and white-yellowish nodular or linear areas, adherent to the mucosa. Liver — dark-red, smoothy surface; on cut section, uniform aspect and bile impregnation; normal extra-hepatic bile ducts (W.: 55g; N.: 59.8g). Spleen — enlarged, dark-red; the pulp is firm and uniform (W.: 7g; N.: 4g).

Microscopic examination — Lungs — areas of diffuse or nodular hemorrhages, involving pleura, interstitium and airpassages, allied to others of necrobiosis, where the local structures are faintly visible. On these areas, myriads of delicate bacilli are seen, accumulated preferently on the vascular walls of medium and small vessels, conferring to it a peculiar aspect, smudgy and bluish (H.E.); absence of inflammatory lesions; emphysema. Intestines — congestion of the mucosa with focal areas of hemorrhage and necrobiosis, sometimes involving the muscularis-mucosae; presence of masses of bacilli on the necrotic areas and on the vascular walls; enlarged submucosa with dilated and congested vessels; diffuse mild round cell infiltration; serosa exhibiting dilated and congested vessels, involved by fibrin-leukocyte exsudate. Liver — lobular pattern preserved: portal — spaces of normal size exhibiting mild round cell infiltration, mainly pericanalicular; intraductal bile cast. The intralobular arrangement is unusual: the cellular strands are separated by clear spaces where, in premature, are commonly occupied by foci of erythropoiesis; dilatation and congestion of sinusoids, which contain masses of bacteria. In the hepatic cells pigment, stained partially as hemossiderin, is seen; bile casts in the intercellular capilluli. Spleen — streaks of fibrin adhering to the capsule; paucity of lymphocytes; dilated sinusoids showing occasionally masses of germs; hemossiderin in the pulp. Kidneys — nephrogenic zone present; glomerular congestion; hydropic degeneration of the epithelium of convoluted tubules. Adrenals — capillary congestion where occasionally bacilli are seen. Myocardium — vacuolization and hyalinization of the fibers. Brain — congestion and increased cellularity of the meninges; edema. Presence of masses of bacilli in the capillaries and vessels of the parenchyma.

Anatomical diagnoses — Septicemia due to *Bacillus pyocyaneus* characterized by typical lesions in the lungs, intestines, adrenals, spleen and brain. Bile stasis; absence of hepatic erythropoiesis; hemossiderosis of liver and spleen.

Case II

History — M. J. F. E. (Hosp. 358/62), negro, female, born of normal delivery (1750 g; 44 cm; Apgar 8), twin. Malformed cranium. No abnormalities in the respiratory and circulatory tracts; liver 1.5 cm below the costal rib. On the fourth day she was jaundiced, hypo-

tonic, dispneic, grunting respiration with disseminated pulmonary rales; reflex of suction absent. The weight decreased gradually; no hyperthermia. Death occurred on the fifth day of life.

Necropsy findings — macroscopic examination reveals a mild jaundiced premature with mongoloid facies and muscular rigidity. Absence of the parietal and occipital bones conferring to the cranium a peculiar aspect. The internal examination shows congestion of the meninges and biliary impregnation of the nuclei of the brain, cerebellum and pons. *Thoraco-abdominal cavity* — presence of bloody fluid in the pleural cavities; the lungs exhibit few expanded light coloured patches, intermingled with dark hardened non-crepitant areas. The cut surface has identical aspect (W.: 46.5g; N.: 37.9g). The esophagus and colon show white-yellowish nodular elevated areas, visible even through the serosa; the mucosa of the stomach and duodenum have hemorrhagic aspect. The liver is light-red (3cm below the costal margin), smooth surface. The section show normal lobular pattern and biliar impregnation (W.: 82g; N.: 76.3g). Normal bile ducts. Spleen — dark-red, enlarged; The pulp is uniform and not firm (W.: 9.5g; N.: 4g).

Microscopic examination — extensive areas of resorption atelectasis, with pronounced capillary engorgement and nodular areas of alveolar hemorrhage. Enlargement of alveoli sept-walls with hyperchromasy of alveoli epithelium. Amorphous eosinophil material is seen in the lumen of alveolar ducts with macrophages and desquamated cells. Absence of specific *Pseudomonas* lesions. Esophagus and intestines — congestion of the mucosa; areas of focal hemorrhages and of necrobiosis, sometimes involving all the intestinal coats; absence of leukocytary infiltration. In these areas innumerable delicate bacilli are seen, preferently crowded on the small and medium sized blood vessels; fibrin-leukocytic infiltration in the serosa. Liver — lobular pattern preserved; portal-spaces of normal size; presence of bile casts in the biliar ducts. The intra-lobular arrangement is modified by the existence of clear spaces between the strands of hepatic cells, which would be occupied by erythroblasts. Dark pigment in the hepatic cells, stainable partially as iron pigment; bile thrombi in the capillculi; hypertrophy and hyperplasia of islands of Langerhans. Kidneys — nephrogenic zone present; hydropic degeneration of convoluted tubules epithelium. Myocardium — hyalinization and vacuolization of fibers. Spleen — dilatation and congestion of sinusoids; hemosiderosis. Nervous tissue — congestion and dilatation of vessels of the leptomeninge; pericellular and perivascular edema; degenerative anoxic lesions of the nervous cells; foci of gliosis.

Anatomical diagnoses — Septicemia due to *Bacillus pyocyaneus* characterized by typical lesions in the digestive tract (esophagus and colon) and by isolation of *Pseudomonas aeruginosa* in the lungs. Final lesions of resorption atelectasis; nodular pulmonary hemorrhages. Jaundice. Kernicterus. Bile stasis; absence of hepatic erythropoiesis; hemosiderosis of liver and spleen. Hyperplasia and hypertrophy of islands of Langerhans.

Case III

History — M.J.M.S. (Hosp. 482/62), white, male, born of dystocic delivery (maternal toxemia, abruptio placentae) (1575 g);

39 cm; Apgar 8). On the first three days she presented crises of cyanosis, which disappeared when oxygen was used. On the fifth day she became jaundice, with dyspnoea, vomitings. Posteriorly the respiration was grunting with pulmonary rales. Death on the seventh day of life, with the same symptoms. The weight decreased gradually; no hyperthermia.

Necropsy findings — the macroscopic examination reveals a normal premature exhibiting mild jaundice, yellowish sclera, peroral cyanosis with cyanosis of ungueal beds. A nodular yellowish elevated area (0.5 cm), surrounded by hemorrhagic halo is seen on the tongue tympanism of the abdomen; liver 3 cm below the costal margin; impalpable spleen. Brain — whitish leptomeninge, exhibiting dilated and congested vessels. Bile impregnation of the gray nuclei of the brain, pons, medulla oblongata and cerebellum. *Thoraco-abdominal cavity* — Lungs — dark-red with few light-red areas, without crepitation. Nodular yellowish areas delimited by hemorrhagic halo are seen on the subpleural zone and on cut section. The esophagus, stomach and intestines exhibit identical lesions to the one described on the tongue. Liver (W: — 62 g; N — 66.3 g), dark-red with mottled aspect. On cut section lobular pattern is visible; normal biliary extra-hepatic ducts. Spleen — (W. — 5 g. — N. — 4 g), dark-red; the pulp shows uniform aspect.

Microscopic examination — Lungs — extensive areas of necrobiosis and hemorrhages, involving all the local structures, where myriads of Gram-negative bacilli are seen, preferently accumulated on the medium and small blood vessels; few areas of acute bronchopneumonia. Tongue and pharynx — focal areas of necrobiosis allied to *Pseudomonas* vascularitis, unaccompanied by leukocytary infiltration. Liver — lobular arrangement preserved; normal portal-spaces exhibiting round cell pericanalicular infiltration; the intralobular structure is modified by the presence of clear spaces between the cellular strands, which would be occupied by erythroblasts; scarce foci of erythropoiesis. Presence of dark pigment on the hepatic cells, stainable as iron pigment; pronounced intracellular and intracapillary bile stasis; hypertrophy of Kupffers's cells. Kidneys — nephrogenic zone present; areas of cortical necrobiosis involving glomeruli, tubuli and interstitium, accompanied by *Pseudomonas* vascularitis. Esophagus stomach, and intestines — areas of necrobiosis involving the mucosa and submucosa or all the coats, accompanied by *Pseudomonas* vascularitis. Spleen — paucity of lymphocytes; dilated and congested sinusoids; areas of focal necrobiosis allied to necrotic vascularitis; hemossiderosis. Nervous tissue — increased cellularity of the meninge, which exhibits congested vessels with perivascular hemorrhages; degenerative lesions of anoxic type of the nervous cells.

Anatomical diagnoses — Septicemia due to *Bacillus pyocyaneus* with specific lesions in the digestive tract (tongue, esophagus, stomach and intestines), lungs, kidneys and spleen. Jaundice. Kernicterus. Bile stasis. Hemossiderosis of liver and spleen.

Case IV

History — R. M. S. (Hosp. 684/62), white, male, born of normal delivery (maternal toxemia), (1850 g; 43 cm; Apgar 7). No abnor-

malities on the first day, unless edema of the legs and cervical region, which became generalized in 48 hours, when he exhibited jaundice. On the fourth day he began to vomit, with crises of oral and acrocyanosis, dyspnoea and cutaneous nasal lesions. The symptoms aggravated and he died on the fifth day. The weight decreased gradually; no hyperthermia.

Necropsy findings — the macroscopic examination reveals a normal premature, exhibiting mild jaundice, yellowish sclera, cyanosis of ungueal beds and peroral and a necrotic and ulcerative lesion (0.5 cm) on the left nostril. Whitish-yellow-nodular elevated areas are seen on the tongue. Spleen and liver — palpable below the costal margin. The internal examination reveals the presence of kernicterus with bile impregnation of the nuclei of brain, medulla oblongata and cerebellum and ventricular hemorrhage. *Thoraco-abdominal-cavity* — well expanded lungs; pleural cavities empty; liver and spleen exceeding the costal margin 3 cm and 1 cm respectively. Lungs — the whole organ is dark-red and of uniformly increased consistency; only the anterior parts of lobes are light-red and crepitant. Esophagus — an extensive yellowish-white elevated area on the lower two thirds is seen. The duodenum, stomach and intestines exhibit an extremely congested mucosa. Liver — smooth surface, light-red colour, normal consistency; on cut section, bile impregnation. Spleen — enlarged, wrinkled capsula, dark-red colour; follicular structure visible.

Microscopic examination — Lungs — interstitial diffuse round-cell infiltration; a few areas of necrobiosis and acute bronchopneumonia. Liver — lobular structure preserved; periportal areas of necrobiosis attaining structures of portal-spaces and hepatic cells, with *Pseudomonas* vascularitis; intracellular and intracapillar bile stasis; scarce erythropoiesis; hemossiderosis. Kidneys — nephrogenic zone present; hydropic degeneration of the convoluted tubules. Spleen — paucity of lymphocytes; hemossiderosis. Esophagus and tongue — extensive areas of necrobiosis involving the superficial areas with necrotic vascularitis. Intestines — focal areas of necrobiosis in the mucosa and muscularis-mucosae; necrotic vascularitis. Pancreas — hypertrophy and hyperplasia of the islands of Langerhans, with focal areas of hemorrhages; presence of blood in the ventricular cavity; degenerative anoxic lesions of the nervous cells; foci of gliosis.

Anatomical diagnoses — Septicemia due to *Bacillus pyocyaneus* with specific lesions on the nostril, digestive tube (tongue, esophagus, intestines), liver and lungs. Jaundice with kernicterus; ventricular cerebral hemorrhage. Bile stasis. Hemossiderosis of the liver and spleen.

COMMENT

The analysis of the presented cases shows that all of them were prematures born in fairly good conditions, the infectious symptomatology having developed after the third day of life, an argument favorable to its extrauterine origin. In all of them a very rapid course of the disease was verified, confirming the severity of *Pseudomonas* infection of the newborn, a fact stressed by numerous authors.

Both gross and microscopic examinations revealed multiple visceral lesions, peculiar to the infection by this organism. The common aspect of the focal infection produced by *Pseudomonas aeruginosa*

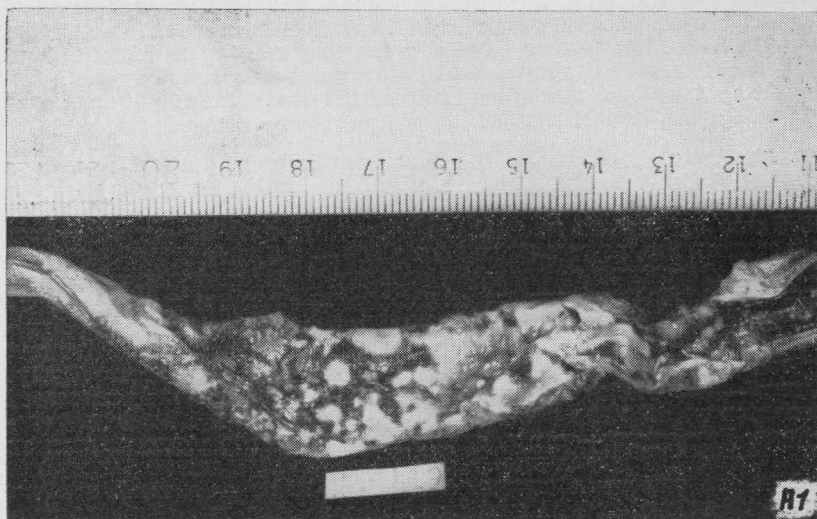


Fig. 1 — Case II: areas of necrobiosis in the colon.

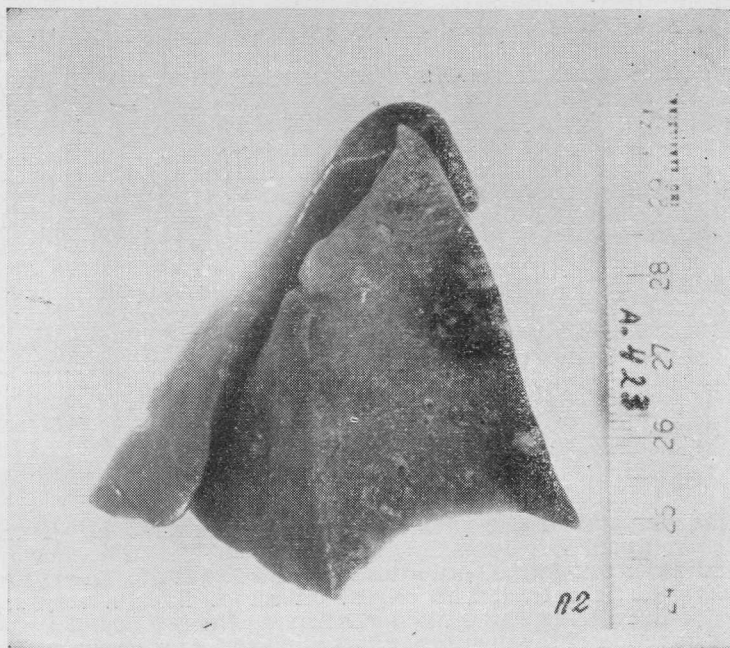


Fig. 2 — Case III: presence of nodular yellowish areas delimited by hemorrhagic ones in the lungs.

was observed in all of the four cases — extensive areas of necrobiosis where the local structures, although modified by the coagulative necrosis, were not totally impaired, allied to the absence of purulent process and commonly accompanied by hemorrhages. Fraenkel (6, 7, 8, 9) considers that the necrotic lesion results from the local toxic action of the bacteria and may become purulent, a fact which we did not observe in any of visceral localizations. Some authors (18, 19, 20) stress that the absence of phagocytosis by polymorphonuclears seems to indicate that the resistance to Gram-negative bacilli may be due to humoral mechanism rather than to the cellular one. Stanley (21) refers to the production of proteolytic enzymes as responsible for the necrobiotic areas. By experimental studies in rabbits, Clément and Millard (22) reproduced *Pseudomonas* lesions identical to the human ones, using bacterial filtrates, confirming the existence of proteolytic and hemolytic toxins responsible for the hemorrhagic and necrotic type of lesions.

The peculiar aspect of vascular lesions, so masterly described by Fraenkel (6, 7, 8, 9) and considered by him pathognomonic of *Pseudomonas* septicemia, was verified in all of our cases, on the multiple attained viscera. However, in case I, only the lungs presented typical lesion — extensive areas of necrobiosis, allied to impairment of the medium and small vessels, which exhibited bluish and smudgy aspect, occasioned by the crowding of the bacilli on the media and adventitia: in the other visceral localizations of the process, as adrenals, liver, spleen and brain, only masses of microorganisms were seen in the lumen of the vessels, without vascular lesions or of their dependent structures. After Rolly (5) the passage of *Bacillus pyocyaneus* through the intima and media of the vessels is unques-

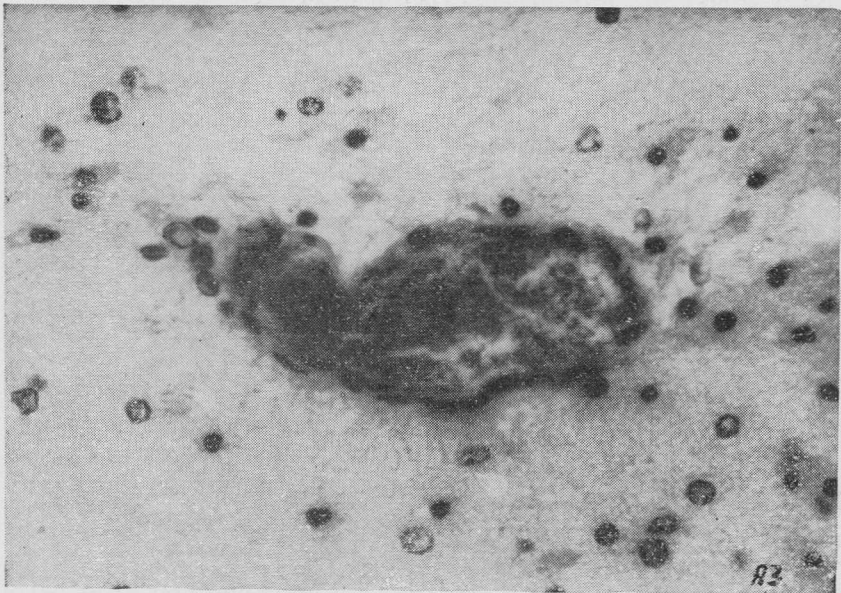


Fig. 3 — Case I: Presence of bacilli in the lumen of a cerebral vessel.
(Leitz: Oc.: 9; Obj.: 45)

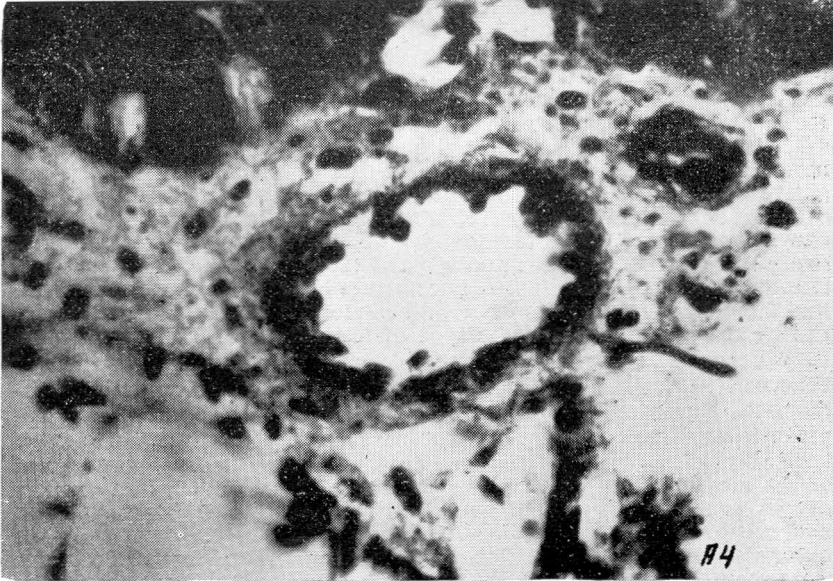


Fig. 4 — Case III: Specific vascular lesion in an esophageal vessel. The bacilli are accumulated on the vascular wall and on the vicinity of it. (Leitz: Oc.: 9; Obj.: 45).

tionable. He stresses that the vascular obliteration by embolic process, interrupting the local circulation, allied to rapid bacillar proliferation, produces lesions on the vascular wall, ensuing the penetration of bacteria on the boundary tissues with focal areas of necrobiosis. Margaretten (23) analysed the peculiar lesions of *Pseudomonas* septicemia and reminded that the pathological findings suggest that the lesions develop from inside to outside of the vessels. If this baby had lived longer typical lesion would have probably develop in the organs where only masses of bacteria were visualised in the vascular lumen. Some authors (23, 24, 25) accentuated that it is through a capsular polysaccharide that the bacillus adheres to the vessel and enzymes, as hyaluronidasis and necrotizing proteases, may find substrate on the vascular walls themselves. Fisher (26) considered that the collagenase produced by this bacillus breaks the tissular defenses and propitiates the vascular involvement.

Only in one case we were able to obtain hemoculture, but as assured by Fraenkel (6, 7, 8, 9), the vascular lesions may permit the diagnosis of *Pseudomonas* septicemia even without hemoculture.

In reference to the primary lesions we must stress that the digestive lesions were very extensive and diffuse, with involvement of the tongue in two cases (Cases II and IV) permitting the assumption that the contamination may have occurred by this route. The esophagus was severely involved in three cases, contrasting with Fraenkel's cases (6, 7, 8, 9), where he did not report esophageal lesions. Only in one case gastric lesions were found (Case IV).

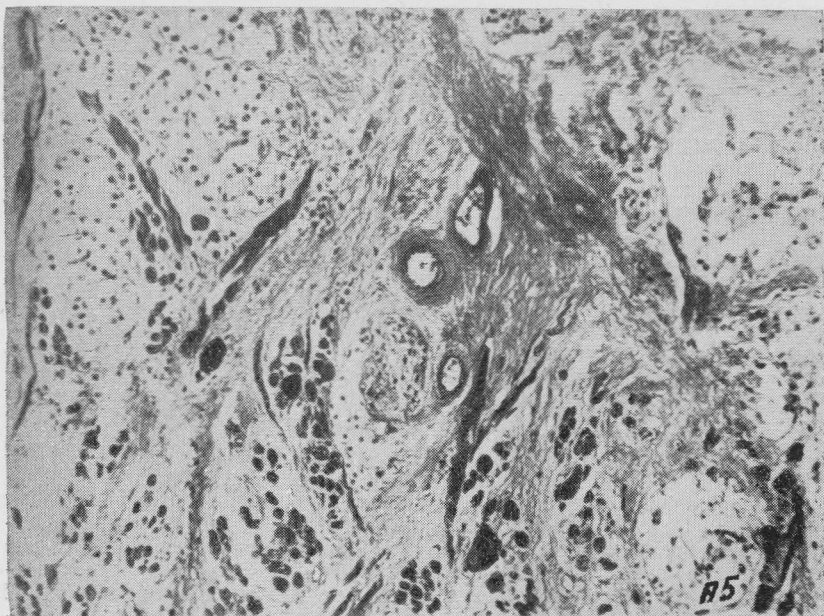


Fig. 5 — Case IV: Area of necrobiosis involving the local structures in the tongue with typical vascular lesion. (Leitz: Oc.: 9; Obj.: 10).

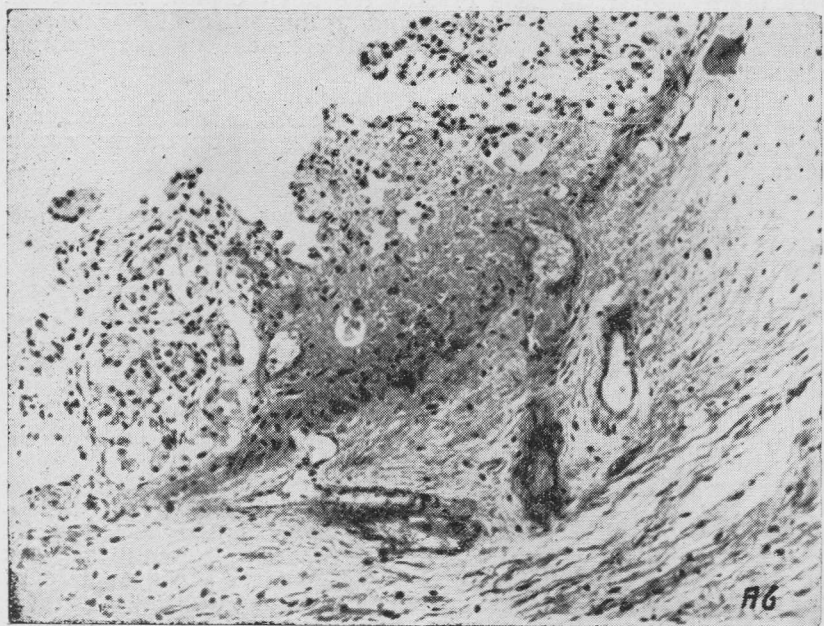


Fig. 6 — Case II: section of the intestine showing a cuneiform necrobiotic area located in the mucosa and muscularis-mucosae accompanied by local *Pseudomonas* vascularitis. (Leitz: Oc.: 9; Obj.: 10).

Gross examination, in all cases, reveals very similar lesions in the digestive tube, as well limited whitish elevated nodular areas, visible in the mucosa and, sometimes, through the serosa. At all times we found this macroscopical aspect, the pyocyanus was identified on microscopical examination. It is our opinion that this aspect is peculiar to *Pseudomonas* infection. Fraenkel (6, 7, 8, 9) considered that the intestinal lesions may be highly suggestive of this type of infection, although these did not offer the accuracy of diagnosis of the cutaneous lesion — the *ecthyma gangrenosum*. In what concerns the microscopy, the lesions have equally an identical aspect — necrobiotic areas crowded with bacilli located on the superficial coats or involving all the intestinal wall. The *Pseudomonas* vascularitis was constantly observed. Schaffer and Oppenheimer (27) related cases of intestinal perforation, something which we did not observe. Cathala (28) stressed the prevalence of intestinal symptomatology mainly with the younger; the paucity of clinical history in our cases could not permit us to evaluate this assertion.

Only one case (Case IV) presented a necrotic area on the nostril; no other cutaneous lesions were verified.

The gross examination did not reveal specificity as to pulmonary lesions. Is Case III nodular, elevated, whitish areas, limited by hemorrhagic halo, were verified on the subpleural area and in the interior of the parenchyma. These, allied to the digestive ones, permitted the diagnosis. The microscopic examination showed areas of necrobiosis and hemorrhages accompanied by *Pseudomonas* vascularitis. Hemorrhages predominated in Case I; the areas of necrobiosis were smaller and rarer and the vascular involvement more discrete. It seems to correspond to the type of hemorrhagic bronchopneumonia described by Wassermann (4). There were no specific lesions in Case II; in Case IV only the microscopical examination revealed focal areas of necrobiosis and an interstitial diffuse process, also quoted by Cremer (29). Pleural effusions or parenchymal abscesses were not visualised.

Discrete splenomegalia was present in all cases. Rolly and Stanley (5, 21) think that it is always present in the *Pseudomonas* septicemia. The microscopy showed specific lesions in two cases: intravascular masses of bacilli in Case I and necrobiotic areas with vascularitis in Case III.

Renal lesions — necrobiotic cortical areas allied to the involvement of the corresponding vessels, typical of the septicemic process, were observed only in Case III.

Jaundice and hemolysis were constantly verified, characterized by bile stasis, liver and spleen hemossiderosis and paucity of extramedullary erythropoiesis. In fact, the peculiar microscopical aspect of hepatic parenchyma was unusual. The hepatic cellular strands were separated by clear spaces which ought to have been occupied by erythroblasts. We believe that absence of foci of erythroblastic cells is caused by hemolysis and depletion of bone marrow, a fact already stressed in the *Pseudomonas* septicemia (14, 17, 23, 30).

Noteworthy is the presence of kernicterus in three cases (Cases II, III, IV). Forkner (14), after identifying nervous lesions in 65% of his 23 cases, emphasized the neurotoxicity of *Pseudomonas*; he also asserted that Charrin and Jadrewitsch assumed identical point of view. The nuclear impregnation, probably, is a consequence of hemolytic and neurotoxic action of the *Bacillus pyocyanus* toxins.

We did not find involvement of the meninges in the pathologic process. In Case I the capillaries and vessels of the brain had the

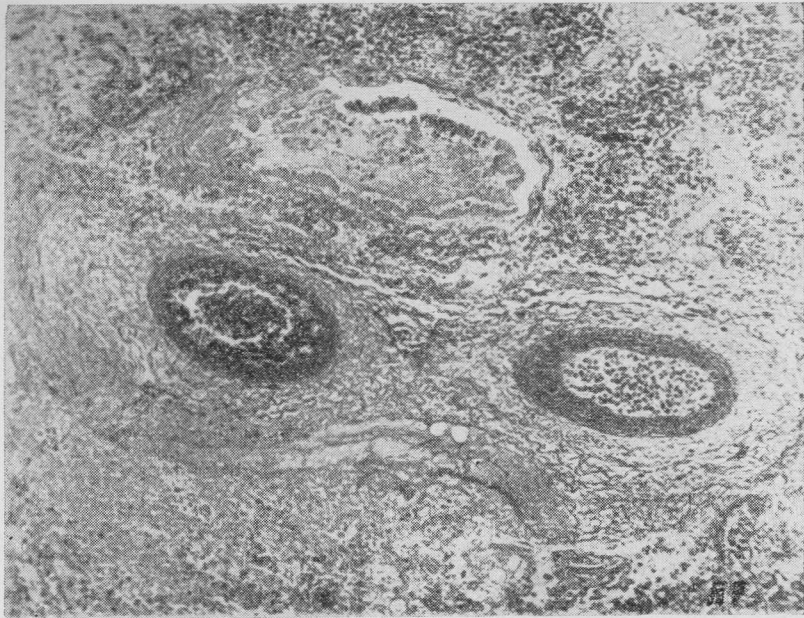


Fig. 7 — Case III: Extensive area of necrobiosis in the lung. The peculiar aspect of *Pseudomonas vascularitis* is well seen. (Leitz: Oc. 9; Obj.: 10).

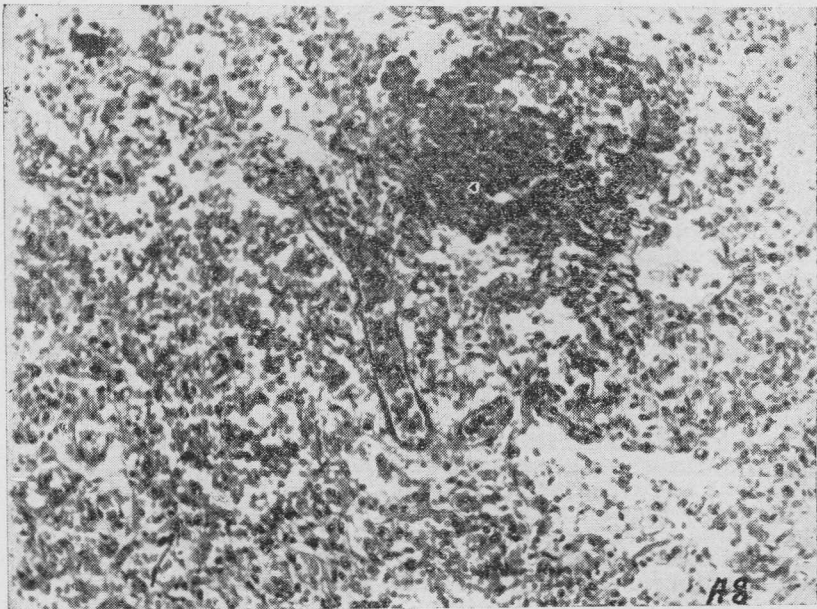


Fig. 8 — Case I: Section of the lung exhibiting necrobiosis of the alveolar wall in decurrence of specific vascularitis. (Leitz: Oc. 9; Obj.: 10).

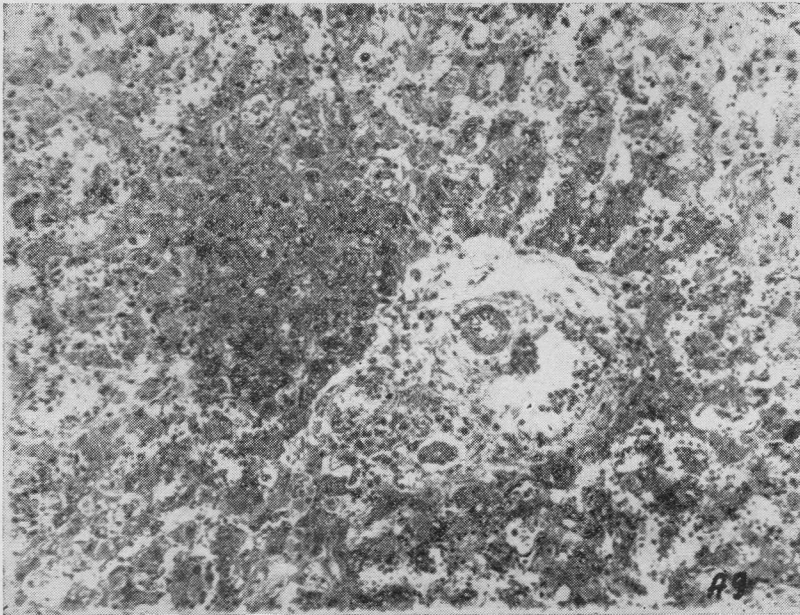


Fig. 9 — Case I: Presence of a nodular periportal area of necrobiosis. The strands of hepatic cells are separated by clear spaces; scarce erythropoiesis. (Leitz: Oc. 9; Obj.: 10).

lumen occupied by masses of bacteria, but no vascular lesion or of the nervous tissue were found. In Case IV, not only kernicterus, but also ventricular hemorrhage was verified.

SUMMARY

A histopathologic study of four cases of *Pseudomonas aeruginosa* septicemia in the newborn is presented. All of these cases refers to prematures born in fairly good conditions, their symptomatology having appeared after the third day of life, a fact which accounts for the extra-uterine origin of the disease.

In all of them peculiar visceral lesions were observed extensive areas of necrobiosis crowded by microorganisms, along with hemorrhagic ones, free from inflammatory reaction and always accompanied by a necrotic vascularitis. The accumulation of myriads of delicate bacilli on the media and adventitia of the blood vessels confers to the attained vessels a peculiar aspect, which is commonly considered as pathognomonic of the *Pseudomonas* septicemia.

Probably the digestive lesions should occur in the first place, as they proved to be largely disseminated and extensive, emphasizing the involvement of the tongue in two cases. The esophagus was severely attained in three cases and the stomach only in one. Intestinal lesions were constantly observed, showing a peculiar macroscopic aspect, seeming to be typical of *Pseudomonas* infection.

The gross pulmonary lesions had no specific aspect, and only in one case a diagnosis could be assumed when simultaneous digestive lesions were also taken into consideration. Furthermore microscopic examination revealed typical lesions in two cases, absence of specific lesions in another case and the presence of the interstitial type of the pulmonary *Pseudomonas* infection in the last one.

Splenomegaly was always observed; typical microscopical lesions having been verified in two cases.

Renal lesions, as typical of *Pseudomonas* septicemia, were seen in only one case.

Macroscopic examination of the liver was inexpressive and microscopic inspection showed typical necrobiotic areas only in one case, accompanied by specific vascularitis. It is noteworthy in all the cases the absence or scarce hepatic erythropoiesis, a fact we attribute to the depletion of the bone marrow. Hepatic bile stasis and hemossiderosis were constantly verified.

It was remarkable that the presence of kernicterus occurred in three cases, the cause of which may be linked to the hemolytic and neurotoxic action of the *Bacillus pyocyaneus* toxins.

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