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Dysentery and Colienterocolitis

Some Aspects of Pathogenesis and Pathological Anatomy

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Summary. The author studied 112 autopsied cases of dysentery and colienterocolitis (intestinal coli infection) in children and the intestines of 80 rabbits intoxicated with Shigella and Escherichia coli in the isolated loops of rabbit intestine (De and Chatterjee method).

It was shown that reproduction of the causative agents of both diseases occurred mostly in the intestine lumen and that Shigella bacilli and pathogenic Escherichia coli themselves caused only catarrhal inflammation but along the whole length of the intestine. Acute ulcerative or fibrinonecrotic processes in the cases investigated usually occurred only in combination with staphylococcus infection or candida mycosis of the intestine. Some ulcers in the intestine were due to vascular disturbances.

Zusammenfassung. Zur Untersuchung gelangten 112 Sektionsfälle mit Ruhr und Colienterocolitis im Kindesalter. Außerdem wurde der Darm in 80 nach De und Chatterjee infizierten Kaninchen untersucht. Es wurde gefunden, daß die Vermehrung der Erreger beider Krankheiten hauptsächlich in der Darmlichtung stattfindet und die Schigellen und pathogenen Escherichien nur eine katarrhalische Entzündung entlang der ganzen Ausdehnung des Darmes hervorrufen. Die eitrig-fibrinöse Entzündung und akute Ulcerationen wurden in den untersuchten Fällen in Kombination mit Staphylokokkeninfektionen oder mit Candidamykosen des Darmes beobachtet. Ein Teil der Ulcerationen war, wahrscheinlich, durch Blutzirkulationsstörungen verursacht.

Bacterial intestinal infections occur rather frequently in children and that's why are studied at large. A great number of works deals with pathological anatomy of these diseases, especially dysentery (Dopter, 1903; Lorentzen, 1923; Huebschmann, 1925; Blacklock, Guthrie, 1937; Letterer, 1944; Afanasjeva, 1959; Mironchik, 1961; Braun, 1963; Tikhonova, 1964; Bibinova, Ariel, 1964, and others). But as it had been impossible to isolate in tissues pathogenic bacilli of intestine bacteria family from nonpathogenic ones and as there had been some difficulties in defining the possible significance of other microflora, practically all investigators didn't study each change revealed in the intestine separately but considered them to be characteristic of one or other intestinal infection. It depended upon what agent from a number of pathogenic enterobacteria had been isolated by microbiologists. Up to the present time practically in all manuals (Felsen, 1945; Merkel, 1956; Rezek, Millard, 1963; Boyd, 1965; David, 1970; Strukov, 1971, and others) it has been pointed out that the most typical changes are in dysentery—fibrinous or ulcerative colitis and in colienteritis—catarrhal enteritis.

This difference in localization and character of lesion incomprehensible since these diseases are caused by similar bacteria. It can't be explained by the difference in the place of reproduction of Shigella and Escherichia. Things stated above necessiate a further study of dysentery and colienterocolitis.

Materials and Methods

The results of 112 autopsied cases of dysentery and colienterocolitis in children proved by bacteriological investigation were used in this study. Some autopsies were made in 1958–1971 by the investigators themselves and some materials of the autopsies made by other prosectors, including the years 1930–1940, had been used for a deeper histological investigation.

The main difference of this work from the majority of other researches is the attempt to delimit the changes in tissues caused by different microorganisms, just as it has been done by us in the study of respiratory infections (Zinserling, 1970, 1972).

For this purpose intestine specimens were constantly stained not only by means universally adopted in histological investigations, but by different histobacterioscopic methods as well.

During light microscopic investigation staining by azur-eosine, by Schiff and Shabadash, Gram and Weigert and sometimes others stains were used. Immunofluorescent research by the direct Coons method was constantly carried out. After revealing this or that microorganism, their interactions with the tissues of the organism were defined as far as possible in particular the cell reaction on these microorganisms.

To make some sides of morphogenesis more precise, the further study of experimental shigellosis and escherichiosis in the isolated loops of 80 rabbits was carried out. This model was first suggested for the investigation of cholera by Violle and Grendiropoulo (1915) and later elaborated by De and Chatterjee (1953); in medical literature it is known as the model of De and Chatterjee or the model of De.

Results

Uncomplicated Dysentery. After detailed study of 53 autopsied cases of dysentery in children in their first months or years of life (Leontiev, 1970; Zinserling and Leontiev, 1970) we first of all singled out a group of 14 patients who showed during histobacterioscopic investigation only gramnegative bacilli (Shigella and unmarked intestinal) in the intestine as a rule. The lesion of intestine in these deceased was comparatively slightly marked.

When intestine was histologically investigated, desquamated epithelial cells, mucus and separate leucocytes and sometimes erythrocytes as well as a considerable amount of microbes with sharp predomination of gramnegative bacilli were found mainly in the lumen of large intestine. In case of death at early stages of the disease a considerable number of Shigella could be seen among them; which can be proved by the results immunofluorescent microscopy (Fig. 1 c).

In the intestine, especially in the distal parts of the large one, dystrophic changes of epithelial cells were revealed and an increased content of mucus was noted in particular (Fig. 1 a, b). Rather many mitoses, especially in cripts were not uncommon. Desquamation of epithelium in small intestine was defined chiefly on the fibres, that were changing their regular form because of that.

The stroma of the mucosa was moderately congestive, oedematous, unequally infiltrated by cells, chiefly by lymphocytes and later by plasmatic cells and histiocytes as well as by neutrophil leucocytes (Fig. 1 a).

There was a moderately marked oedema and a slight cell infiltration in the submucous membrane chiefly around the vessels as well as in the areas adjacent to mucous membrane or folliculus. Circulatory disturbances were noted in mucous and serous membranes.

Lymphatic follicules were large, usually with great centers of reproduction and a considerable number of mitoses. Not uncommonly decomposition of single lymphocytes and reticular cells was noted.

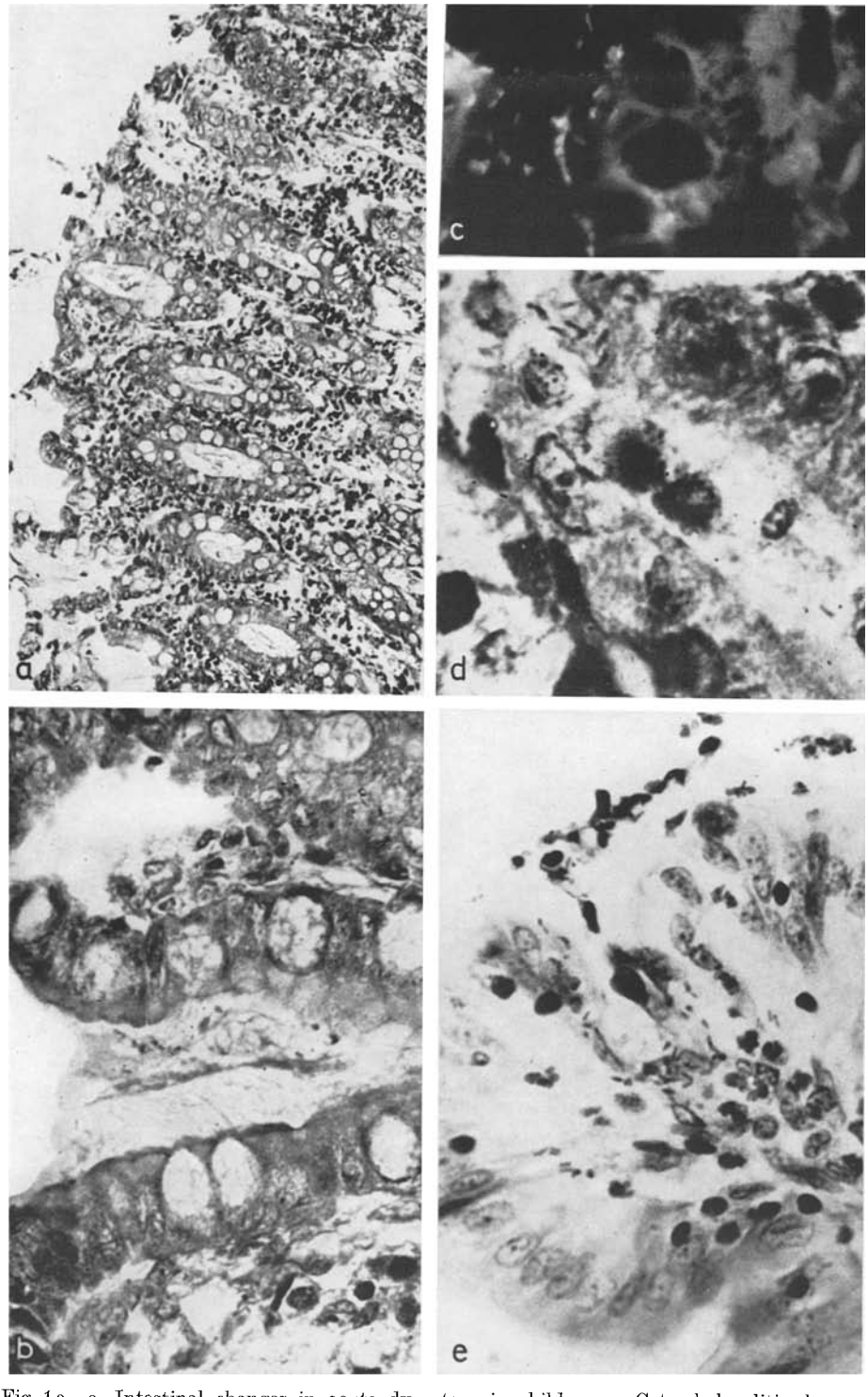

Fig. 1a—e. Intestinal changes in acute dysentery in children. a Catarrhal colitis, hypersecretion of epithelium, azur-eosine. ×135. b Detail of the proceding preparation, gram-negative bacilli are seen in the lumen. ×900. c Shigella in the intestine lumen, the preparation is treated by specific fluorescent serum. d There is a group of Shigella in one of the epithelial cells, azur-eosine. ×1300. e Experimental Shigellosis (model De and Chatterjee)—invasion of Shigella into submucous membrane through the injured epithelium, azur-eosin. ×900

Macroscopically the mucous membrane of small intestine in such children was found to be as a rule thin, glossy, bloody with reddish crowns and patches around lymphatic follicules. The mucosa of large intestine, especially of their distant parts was changed more considerably. It was usually reddish, oedematous, congestive, sometimes with minute haemorrhages. In the intestine lumen there were yellowish and greenish liquid masses, rarer of watery character. There were usually rather many clots of mucus and sometimes traces of blood.

Thus is all cases where lesion of the intestine was caused solely by Shigella (Sonne, Flexner) it might be evaluated only as catarrhal enterocolitis.

In other children in the parts of intestine with progressive inflammatory changes not only Shigella but other pathogenic microflora was revealed which participated in causing enterocolitis. These changes will be discussed later.

Taking into consideration the viewpoints that intraepithelial reproduction of Shigella is of great importance in the pathogenesis of dysentery, we investigated this phenomenon with due attention. Summary data of all 53 observations are given in the Table 1.

Table 1. Frequency and degree of manifestation of intraepithelial location of Shigella

Duration of the disease (in days)	Distribution of Shigella in cytoplasm of intestinal epithelium			In all
	small group in single cells	single in a preparation	is absent	
1–3	0	3	10	13
4–6	1	2	1	4
7–10	2	2	2	6
11–15	1	4	1	6
16–20	2	0	2	4
>20	2	5	13	20
Total	8	16	29	53

Thus intraepithelial distribution of Shigella was irregular, being most often revealed in separate, chiefly desquamating cells of intestinal mucous membrane (Fig. 1 d) and at a different period of time after the start of the disease.

It suggests the fact that such a location of Shigella was occasional and that intraepithelial reproduction of Shigella is of little importance in dysentery pathogenesis.

Principally the same changes were revealed by Avramenko (1972) together with Ioakimova in the study of experimental Shigellosis Sonne on the model De and Chatterjee. In this case in ligated intestinal segments of a rabbit alongside with circulatory disturbance dystrophic and later necrotic changes of intestinal mucous membrane there occurred moderate inflammatory changes in the stroma of mucous and submucous membrane as well. Liquid content was accumulated in the intestine lumen but missing in the control segments of the same rabbit. This content consisted of mucus, cell detritis, layers of desquamated epithelial cells, macrophages. Shigella reproduction occurred in the intestine lumen and only later these bacteria spread into the stroma of mucous membrane through the lesioned portion of mucous membrane (Fig. 1 e).

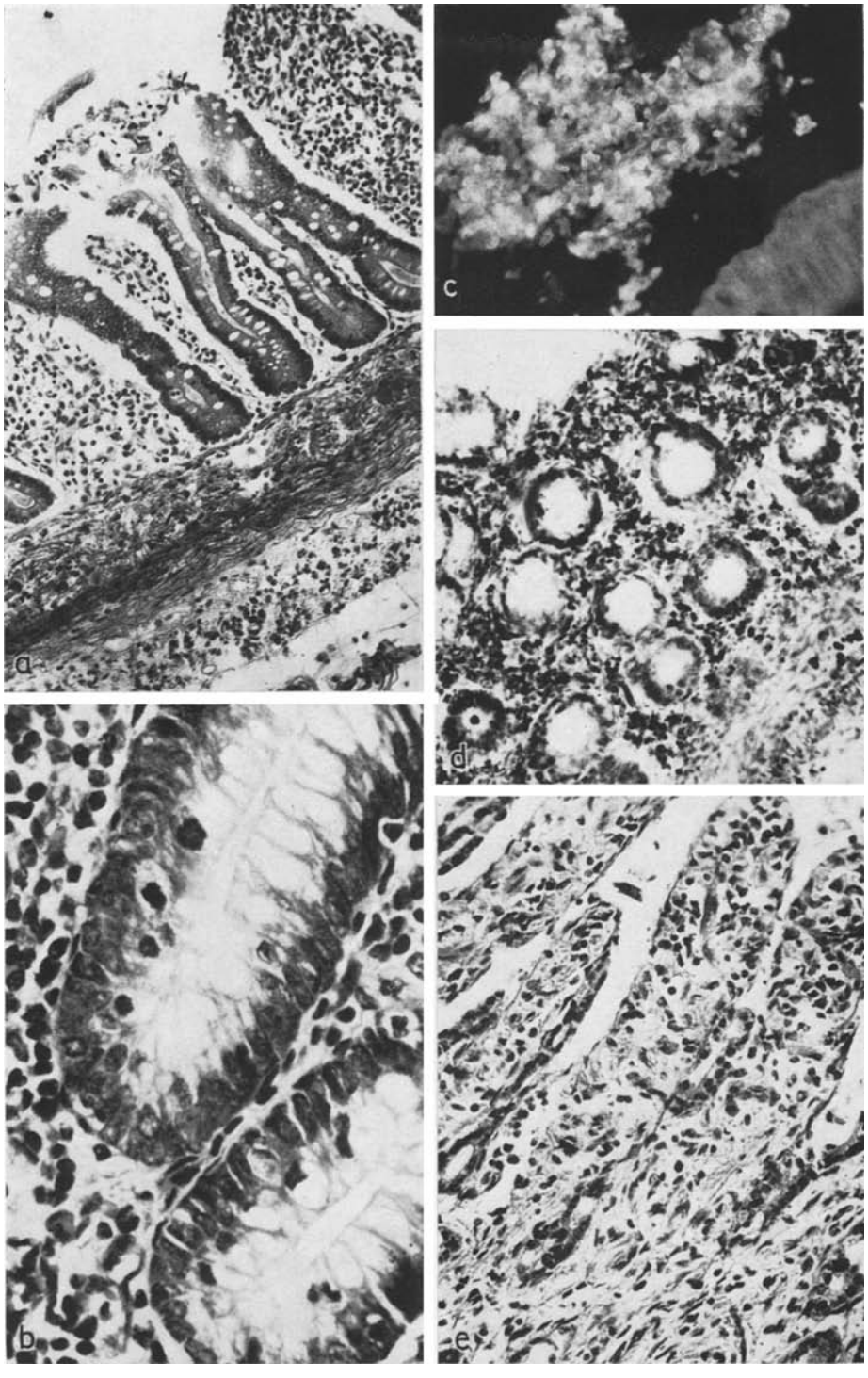

Fig. 2a—e. Intestine changes in colienterocolitis (intestinal coliinfection): a Catarrhal enteritis, H.-E. × 135. b Detail of the preceding preparation—a large number of mitoses. × 900. c Accumulation of PEC 0111 in the intestine lumen, the preparation is treated by specific fluorescent serum. d There is a considerable leucocytic infiltration in the intestine stroma, stained by Goldman. × 135. e Regeneration of the mucous membrane, H.-E. × 300

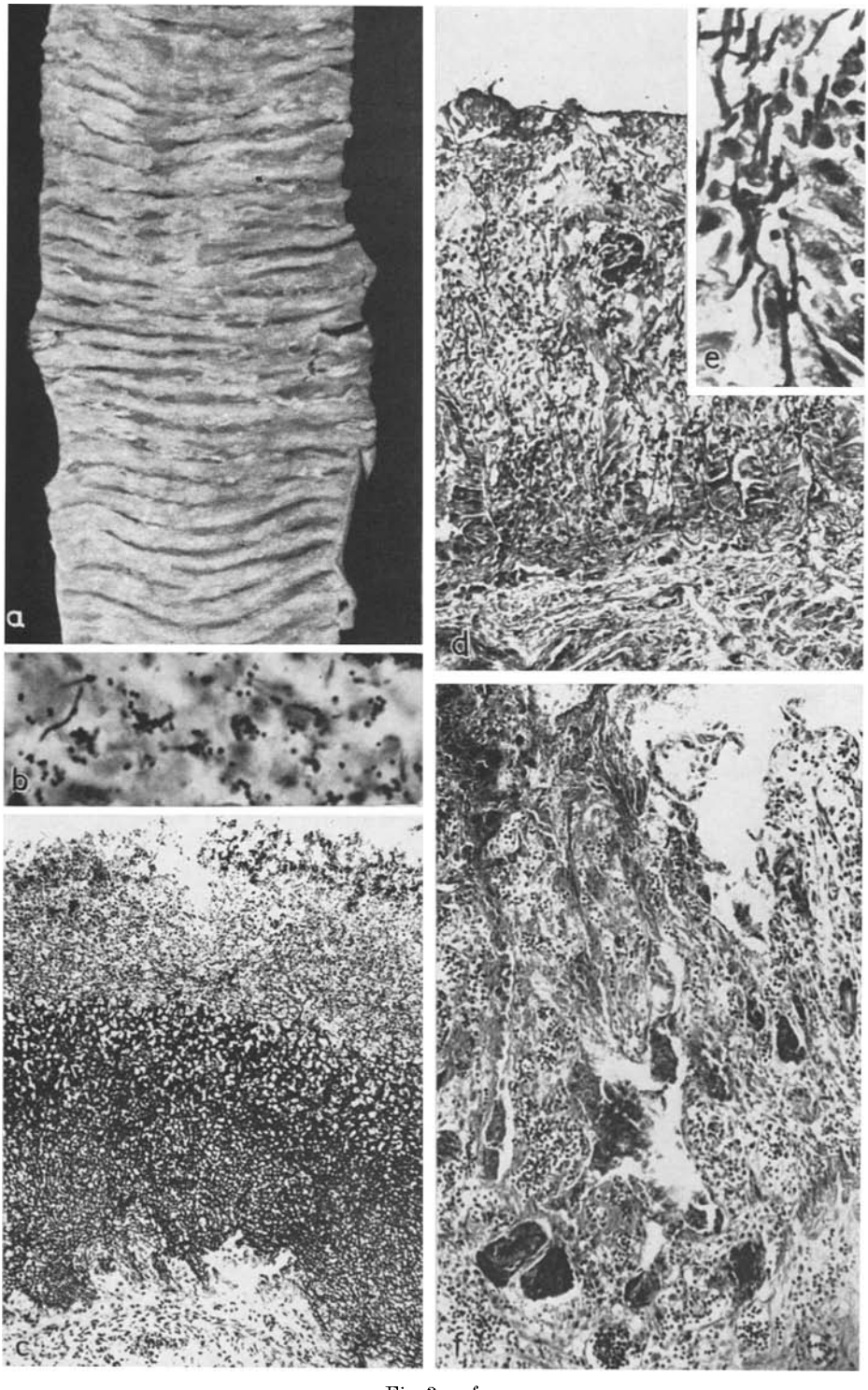

Fig. 3 a—f

These experiments firstly confirm the above stated viewpoint that Shigella intraepithelial reproduction is of no essential importance for dysentery pathogenesis and, secondly, show that liquid content in dysentery is not so much the result of absorption failure but that of exudation.

Uncomplicated Colienterocolitis (intestinal coliinfection). The author has studied in detail 58 autopsied cases of colienterocolitis induced for the most part by pathogenic Escherichia coli (PEC) 0111 in children chiefly in the first months of their life (Zinserling *et al.*, 1968).

In 32 children who had died in the acute form of the disease only Escherichia coli (pathogenic and nonpathogenic) were revealed in intestine when histobacterioscopic investigation was made. Intestinal changes in all these patients were relatively slight.

Histological research of intestinal lumen reveals protein flakes, cells of desquamated intestinal epithelium and different number of various microbes, gram-negative bacilli considerably predominating. Sometimes practically they present PEC which can be clearly seen during the immunofluorescent research (Fig. 2c).

In the wall of intestine, chiefly in the small one, distinct changes were defined mostly in the epithelium that was subjected to dystrophic changes and was often missing on the surface. In cripts a great number of mitoses in the form of a star was constantly revealed (Fig. 2b). We failed to find any microbes in the epithelial cytoplasma. The height of the fibres is unequal, they are mostly low, sometimes sharply defined.

In the stroma of the mucous membrane moderate circulatory disturbances and sometimes fine haemorrhages were observed. The stroma is often rich in cells—lymphocytes, plasmatic and histiocytes (Fig. 2a). Not uncommonly some small accumulations of neutrophil leucocytes were observed (Fig. 2d).

In the submucous membrane some focus plethora, oedema and sometimes round cell infiltration were noted.

In large intestine the same changes were usually observed, though they were much weaker. Besides, gobletcells were determined here in greater number than usual.

Lymphatic apparatus of the intestine and mesentary lymphatic vessels are moderately congestive with enlarged centers of reproduction and also with phenomenon of disintegration of some part of lymphocytes and reticular cells.

Macroscopically these children had moderate focus hyperemia of the small intestine mucous membrane especially ileum and often in the area of Payer's patches and lymphatic follicules. Small intestine was mostly extended, congested with liquid, more often watery content with small green clots of mucus. Similar,

Fig. 3a—f. Intestine changes in complicated dysentery. a Fibrin-ulcerative enterocolitis. b A considerable predomination of staphylococci over microbes in the superficial layers of fibrino-leucocytic masses, stained by Gram and Weigert. × 1350. c Fibrinous colitis with a great number of staphylococci in the superficial layers. The preparation is stained by Gram and Weigert. × 135. d Colitis with the profuse growth of fungi Candida, stained by Schiff and Shabadash. × 135. e A detail of the preceding preparate—Candida pseudomycelium and cells. × 600. f Acute ulcerative colitis, staphylococci predominant at the site of necrosis, azur-eosin. × 135

though weaker marked changes of the mucosa were determined in large intestine. In their lumen there was yellow or greenish yellow liquid content with a little admixture of mucus.

Thus, in all our observations, where the lesion was produced only by pathogenic Escherichia it had the characteristics of the catarrhal enterocolitis. The presence of mucosa regeneration (Fig. 2e) at later stages of this disease is a proof that these are not post mortem changes, as many pathologists supposed, but it is really a process taking place during the lifetime.

When studying experimental Escherichiosis 0124 on the model De and Chatterjee (Avramenko, 1972) the data obtained were principally identical in their results with the experimental Shigellosis. One can only note, that the changes developing in animals, were marked weaker.

Chief Local Complications and Concommitant Processes in Dysentery and Colienterocolitis. Changes of other character besides the above mentioned caused by Shigella and Escherichia may be observed in the intestine of patients with dysentery and colienterocolitis. They can be combined into two groups.

Infection processes of an other different etiology were ascribed to group 1, staphylococcus enterocolitis being of greatest significance among them. In the fact, lesion of such kind occurred in 22 cases, in particular where acute ulceration or phybrino-necrotic colitis and enterocolitis were macroscopically diagnosed (Fig. 3a–c, f). Such changes were revealed in 20 out of 53 children ill with dysentery, proved by bacteriological investigation. These changes were also noticed in 2 children whose disease on the ground of clinical and bacteriological data was considered to be colienterocolitis.

In 3 children the lesion of identical character was due not only to staphylococcus but also to fungi of genus Candida (Fig. 3d, e).

In 29 children including 6 suffering from dysentery and in 25—suffering from colienterocolitis, changes regularly enough discovered in acute viral respiratory infections (AVRI) were revealed (Zinserling *et al.*, 1970). They develop acute, chiefly alterative changes, first and foremost in the cariorexis of the epithelium of intestine mucous membrane and have nothing to do with the period between death and autopsy. It should be noted that simultaneously with these intestine changes, similar in different AVRI, lesions of other organs, chiefly of respiration were revealed and they were often typical of some definite AVRI.

To the second group of processes, revealed in addition to the principal disease (dysentery or intestine coliinfection) some infectious processes may be ascribed. In infants in the first months of their life the development of mucous membrane ulceration was most important. These ulcers, sometimes single ones, more often numerous, were revealed in 5 children. They occurred chiefly in small intestine and were localized along the mesentery attachment or on the opposite side. The bottom and the edges of these ulcerations (diameter of 2–10 mm) were at first formed by the necrotic tissue and later by a thin layer of granulated tissue. In some parts the growing or regenerating epithelium on these parts was noted. Localization of these ulcerations in the segments of intestine vascularized worse than the others, their distribution in chains in the absence of pathogenic microflora in these parts makes us think about their vascular origin. The fact that similar lesions are not uncommon in newborns without intestinal or other infec-

tion proves that above stated viewpoint. In two children intestinal pneumatosis was revealed which may be considered an occasional coincidence.

Discussion

The chief result of these investigations is firstly the revelation of a rather common development of combined intestinal infections. The most serious intestinal lesions are observed in the cases when not only the bacteria of enterobacteria family but also staphylococci and fungi take part in the origin of the process.

It should be noted that the supposition about the essential significance of the secondary microflora that develops on the ground of dysentery, existed long ago (Gross, 1919; Lorentzen, 1923, and others). This entirely corresponds to the modern viewpoint on cholera, when the so-called cholera typhoid is connected with the stratification of secondary, more often staphylococcus infection.

One should not connect with dysentery and colienterocolitis, as some investigators previously thought, the fine-grain decomposition of epithelium since it is regularly met with in viral respiratory infections, at any rate in children in the first months of life.

These investigations allow not to regard the ulcers along the mesentery attachment or on the opposite side occurring sometimes in children, especially among the newborns, to be the manifestation of dysentery or colienterocolitis. These ulcerations often occur without the above mentioned intestinal infections and they appear most often as a result of vascular disturbances in premature babies with impaired trophics (De Boissière *et al.*, 1961; Waldhausen *et al.*, 1963; Stevenson *et al.*, 1969; Mironchik, 1971, and others). This process is a unique nosologic unit, that is marked by the terms of nonspecific ulcerative enteritis (enterocolitis) of newborns or circulatory hypoergical ulcers of intestine. It should be stressed that this process sharply differs both in pathogenesis and manifestations from nonspecific ulcerative enterocolitis in adults and children of older age (Michener, 1967; Kogoi and Yudin, 1972, and others) at the base of which, as it is stated, are immunomorphological disturbances.

If all the discussed processes are not taken into consideration when evaluating the intestine lesions in dysentery and colienterocolitis, it turns out that for these diseases, at least in children and with the germs that were met with for the last ten years, only catarrhal inflammation is characteristic and it has been observed on the investigated material on the whole extent of intestine. The regularity of small intestine lesions in the dysentery is confirmed during the investigations of the biopsy of this organ (Bluger, Weksler, Novitsky *et al.*, 1973).

Germ reproduction occurs, as a rule, in the intestine lumen. Intraepithelial location and possibly the reproduction of Shigella judging by the results of our investigations occurs unregularly. These data fully correspond to those given in medical literature. There are only a few works which mention that the enterobacteria in the mucous epithelium is revealed. With dysenteria it was described by Lorentzen (1923), Böhmig (1943), Matabeli (1970), Voino-Yasenetsky (1972), Rácz *et al.* (1973) and with colienterocolitis by Ilgner (1956). The majority of these investigators doesn't attach great importance to this phenomenon in pathogenesis of the intestinal infections. Some other authors (Voino-Yasenetsky and

Rácz *et al.*) consider it to play the main role in the pathogenesis of dysentery. But even they don't adduce any facts anywhere concerning the frequency of the phenomenon, particularly about the correlation of the mucous epithelium cells which contain and lack Shigella in the different periods of the disease. According to the statements of some of these investigators they needed a lot of hours to study a great number of preparations to reveal this phenomenon. Things stated above show that in their observations only separate cells of the intestine contained the Shigella. The authors who had studied the dysentery in the monkeys did not make such calculations either (Ogawa *et al.*, 1964; Voino-Yasenetsky, 1966, 1970; Formal *et al.*, 1966; Takeuchi *et al.*, 1967; Ogawa, 1970).

According to our own and literary data we may consider that enterobacteria, revealed in the cytoplasm in any epithelial cells, penetrates there actively. However there are some other opinions as well. Thus Wessel and Rácz (1967) wrote about the active cells phagocytose, that of the cornua epithelium in particular. Though one of these authors in his other articles proved the contrary point of view (Rácz, 1963; Tenner, Rácz, and Sereny, 1970).

The inculcation of enterobacteria apparently takes place in the cells injured before—in the course of their physiological dying off or as a result of having another infection, a viral one in particular. We may suppose that the alterated cells are mainly affected because both in the investigated cases and in the figures adduced (Rácz *et al.*, 1973) by the other authors the Shigella located only in separate cells lying on the surface or already torn away.

Thus, the given short literary information (see the detailed critical review of the works dealing with this question in the article of Zinserling, 1973) confirms the before mentioned point of view that the intraepithelial location and even reproduction of enterobacteria is possible, but the available facts don't allow to attach great importance to it in the pathogenesis of acute dysentery and colienterocolitis.

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