with CD, with or without granulomatous lesions, suggesting that both IL-12 and the lesions are indeed linked to CD (14,15). These data reinforce the idea that focal inflammation of the gastrointestinal tract is a hallmark of CD.

References

1. Schmitz-Moormann P, Maichow H, Pittner PM. *Endoscopic and bioptic study of the upper gastrointestinal tract in Crohn's disease patients.* Pathol Res Pract 1985; 178: 377-387.
2. Maahako MNL, Cezard JP, Navarro J et al. *Crohn's disease lesions in the upper gastrointestinal tract: Correlation between clinical, radiological, endoscopic and histological features in adolescents and children.* J Pediatr Gastroenterol Nutrition 1989; 8: 442-446.
3. Oberhuber G, Puapok A, Oesterreicher C et al. *Focally enhanced gastritis: A frequent type of gastritis in patients with Crohn's disease.* Gastroenterology 1997; 112: 698-706.
4. Wright CL, Ridell RH. *Histology of the stomach and duodenum in Crohn's disease.* Am J Surg Pathol 1998; 22: 383-390.
5. Halme L, Kärkkäinen P, Rautelin H et al. *High frequency of helicobacter pylori negative gastritis in patients with Crohn's disease.* Gut 1996; 38: 379-383.
6. Radford-Smith O, MacGowan I, Jewell DP. *Th1 and Th2 cytokine gene expression in inflammatory bowel disease.* Gastroenterology 1994; 106: A 757.
7. Kuhn R, Lohler J, Rennick D et al. *IL-10 deficient mice develop chronic enterocolitis.* Cell 1993; 75: 263-274.
8. Mizoguchi A, Mizoguchi E, Bhan AK. *The critical role of interleukin-4 but not interferon gamma in the pathogenesis of colitis in the T-cell receptor alpha mutant mice.* Gastroenterology 1999; 116: 320-326.
9. Trinchieri G. *Interkeukin-12: A proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptative immunity* Annu Rev Immunol 1995; 13: 251-276.
10. Wu CY, Demeure C, Kiniwa M et al. *Il-12 induces the production of IFN-y by neonatal human CD4 T cells.* J Immunol 1993; 151:1938-1949.
11. Manetti R, Gerosa F, Giudizi MG et al. *Interleukin-12 induces stable priming for interferon-y (IFN-y) production during differenciation of human T helper (Th) cells and transient JFN-y production in established Th2 cell clones.* J Exp Med 1994; 179:1273-1283.
12. Neurath MF, Fuss I, Kelsall BL et al. *Antibodies to interleukin-12 abrogate established experimental colitis in mice.* J Exp Med 1995; 182: 1281-1 290.
13. Parronchi P. Romagnani P, Annunziato F et al. *Type-i T helper cell predominance and intedeukin-12 expression in the gut of patient with Crohn's disease.* Am J Pathol 1997; 150: 823-832.
14. Berrebi O, Banerjee A, Paris R et al, *In situ RANTES and interferon-y genes expression in pediatric small bowel Crohn's disease.* J Pediatr Gastroenterol Nutr 1997; 25: 371 -376.
15. Berrebi D, Besnard M, Fromont-Hankard O et al. *Interleukin-12 expression is focally enhanced in the gastric mucosa of pediatric patients with Crohn's disease.* Am J Pathol 1998; 152: 667-672.

Childhood gastrointestinal infections and infestations as seen in the tropics

R. Kaschula

Red Cross Children's Hospital and University of Cape Town, South Africa.

The spectrum of infection and infestation that occurs in the tropics is generally not very different from that which is encountered in subtropical and temperate regions but the frequency of particular infections and infestations, as seen in the tropics, varies considerably and also varies from one tropical region to another.

Diarrheal disease

Acute childhood diarrhea is common and is frequently lethal among poor people throughout the tropics. There are many causative agents and the frequency with which they occur varies from area to area and with the season of the year. Viral infections due to Norwalk virus, rotavirus, enterovirus and enteric adenovirus are highly prevalent. Identified bacterial pathogens account for about 30-45% of acute childhood diarrheal disease (1). Particular strains of *Escherichia coli* have an important role and their identification and separation from commensal strains is often a major problem, especially in tropical countries with limited resources. Enterogenic *E. co/i* is a significant cause of diarrhea in children younger than 3 years and also causes traveler's diarrhea in older individuals. Infection generally occurs from contaminated food and water. Enteropathogenic *E.* co/i mainly affects children less than 3 months of age in developing countries. Enteroinvasive *E. co/i* rarely causes epidemics of diarrhea in developing countries and is acquired from contaminated food. Enterohemorrhagic *E. coli* occurs worldwide and causes a watery diarrhea that becomes bloody and is associated with neurologic manifestations. Some strains are associated with the hemolytic uremic syndrome. Enteroaggregative *E.* co/i causes acute persistent diarrhea in infants in developing countries but infection is generally self-limiting. The *Campylobacter* group of organisms is now considered to be the dominant identifiable bacterial pathogen causing severe gastroenteritis in semi-urban shack dwelling children (2) where informal butcheries and home slaughtering of chickens is common practice. During recent years there has been an accumulation of evidence to implicate *C. jejuni* in the occurrence of the acute motor axonal neuropathic form of Guillain-Barré syndrome (3). *Salmonella* and *Shigella* infections in the tropics are no different from those that occur in temperate areas except that they are more prevalent and there is a wide spectrum of virulence. In recent years there have been increased reports of hemolytic uremic syndrome complicating *Shigella* infection. Cholera is becoming more widespread throughout the whole of the tropics and manifests as an acute illness with a rapid loss of fluids and electrolytes from the intestines that leads to hypovolemic shock (4). *Yersinia enterocolitica* gastroenteritis is uncommon in the tropics.

Intestinal tuberculosis

In rural Africa milk is generally not pasteurized and children are increasingly becoming infected with bovine mycobacteria. Such infection usually results in a primary complex occurring in the ileum and mesenteric lymph nodes. However, most cases of intestinal tuberculosis occur as a secondary phenomenon when infected sputum from primary pulmonary tuberculosis from human strains is swallowed. The condition manifests as circumferential ulcers in the lower ileum, caseous mesenteric adenitis and peritonitis. Fibrosis many cause intestinal obstruction and in older children. Rectal infection may cause an schiorectal abscess or fistula.

Tropical sprue

This malabsorption syndrome responds to prolonged antibiotic therapy. It mainly occurs in the Middle East, India and the Caribbean. Patients have watery diarrhea, abdominal discomfort or pain with distention, anorexia, weight loss, glossitis, stomatitis, alteration of skin pigmentation and edema. Persistence of symptoms leads to megaloblastic anemia. Microscopy of intestinal mucosa shows atrophy with an inflammatory infiltrate that includes many eosinophils (5).

Protozoal infections

Giardiasis due to *Giardia duodenalis* is a worldwide disease causing upper abdominal pain and diarrhea or steatorrhea in children. The organisms occur in abundance in the duodenum, common bile duct and upper jejunum. The intestines undergo villous atrophy with excessive loss of surface enterocytes and an accumulation of interepithelial lymphocytes (6). In malnourished or hypogammaglobulinemic children there is reduced production of secretory IgA and nodular lymphoid hyperplasia of intestinal mucosa may occur. The biological behavior of the disease is not significantly influenced by concurrent HIV infection (7). Amebiasis occurs worldwide but is prevalent in the tropics and accounts for many deaths. The controversy as to whether the large and small ameba found in the gut and associated with amebiasis represent different species or distinct pathogenic and commensal forms of the same species *(Entamoeba histolytica* and *E. hartmanni* or *E. dispar)* continues (7) but the balance of evidence points to a single species that changes when enzymes from ingested bacteria and/or host erythrocytes are acquired (8). *E. histolytica* occurs in the lower intestine and colon and release quadrinucleate cysts into the feces. It is estimated that in about 10% of cases with luminal amebiasis the trophozoites become invasive, phagocytose red blood cells and penetrate the colonic wall to cause flask-shaped ulcers and spread through the blood stream to the liver and beyond. In invasive intestinal amebiasis the ameba may also invade retrogradely along the walls of arteries and progressively along the tributaries of the portal vein to cause edema of vessel walls and thrombosis with intestinal infarction and perforation (9,10). In addition, amebiasis may manifest as polypoid structures with many organisms in the cecum of infected children. Rectal amebiasis can involve the anus and perianal skin to produce pseudoepitheliomatous hyperplasia and may rarely become a sexually transmitted disease (11). Amebic liver abscesses that occur as a consequence of hematogenous spread through the portal vein has been seen during the first mouth of life at the Red Cross Children's Hospital. In children there are often multiple small abscesses which rarely perforate. Balantidiasis due to the large protozoan *Balantidium coil* occasionally causes intermittent diarrhea in rural areas after contact with pigs, rats or baboons.

Colonic ulcers are similar to those of amebiasis but may be complicated by hemorhage, perforation or hematogenous spread to liver and genitourinary system. Isosporiasis due to *Isospora bern* is an intestinal opportunistic infection mainly occurring in children in developing countries who are either malnourished or have HIV infection. In common with *Sarcocystis, Cryptosporidium* and microsporidia they cause villous atrophy with an inflammatory cell infiltration into the lamina propria that includes eosinophils. Clinically there is diarrhea, malabsorption and steatorrhea. For diagnosis the parasites may be seen in epithelial cells or oocysts may be identified in Giemsa stained stools. *Cryptosporidium* is a prevalent and underdiagnosed cause of diarrhea in malnourished and immunosuppressed children. The very small organisms occur in intraepithelial vacuoles but are also recognized in stools stained with Ziehl-Nielsen or auramine (12).

Helminthic infestations

Nematode (round worm) infestations are prevalent in tropical and subtropical areas among poor people living in conditions of substandard housing, water and sewage provision. Cestodes (flat worms) and Trematodes (flukes) occur worldwide but are more prevalent among poor people in tropical or subtropical climates. The hookworms, *Ancylostoma duodenale* and *Necator americanus* are indigenous to the moist tropics and particularly occur amongst subsistence farmers. Adult worms live in the lumen of the duodenum below the level of the ampulla of Vater and upper jejunum. They attach to a mucosal villus and suck blood and intestinal fluid. Depletion of iron and protein causes symptoms (13).

Hookworms are a recognized cause of protein losing enteropathy amongst anemic children in the tropics. *Strongyloides stercolaris* has the capacity to undergo successive generations of reproduction within a host so that symptoms may occur years after initial infection when the host could have left an endemic area. Fatal massive autoinfection particularly occurs in immunocompromised hosts (14). Urticarial wheals occur where the infective larvae enter the body through the skin and in heavy infections larvae may cause asthma, watery diarrhea with dehydration and renal failure. Stool larvae may seem to be scanty because of the dilution effect of diarrhea. Secondary Gram-negative septicemia and disseminated intravascular coagulopathy are the most frequent complications and causes of death.

Ascariasis is caused by *Ascaris lumbricoides,* the common large round worm. It is extremely prevalent in moist areas of the tropics and subtropics where up to 100% of children may carry the worm. Heavy infestation is considered to cause nutritional problems, fever, malaise, urticaria, nausea, vomiting, intestinal colic and diarrhea. Complications that occur include: volvulus due to a worm bolus (15); obstructive jaundice and pancreatitis from duct obstruction by one or more worms; cholangitis, liver abscess and hepatic granulomas from embryonating ova may occur subsequently (15,16); irritation and obstructive symptoms occur from worms getting into respiratory passages and eustachian tubes; pneumonitis and bronchospasm attributed to larval migration through the lungs are extremely rare amongst indigenous inhabitants of endemic areas; and mesenteric adenitis has been attributed to infestation and a fatal worm embolus to the lungs has been reported as well as involvement of the kidney and renal pelvis (17,18).

Intestinal capillariasis due to *Capillaria philippinensis* occurs in the Philippines and Thailand with infestation occurring from eating fresh water fish followed by autoinfection. The worms cause abdominal pain, diarrhea, anorexia, nausea and vomiting. Prolonged diarrhea leads to cachexia, muscle wasting and death. Whipworm infestation due to *Trichuris trichiura* is particularly prevalent in Southeast Asia and most infections are light and asymptomatic. In heavy infestation there is colitis with blood and mucus in stools, which can lead to anemia and edema. A tendency to rectal prolapse has been reported and in rare instances acute appendicitis has been attributed to the worm.

Intestinal angiostrongyliasis due to *Angiostrongylus costaricensis* occurs in Central America and *A. cantonensis* in the Far East when man is accidentally infected by ingesting vegetable leaves smeared with the mucus of slugs containing infective larvae. Infected children develop a high pyrexia, anorexia, vomiting, right lower abdominal pain with a blood eosinophilia. The worms lodge in the ileocecal legion producing colonic and intestinal edema with granulomas and lymph adenopathy. The liver, omentum, testes and arteries may become involved in an inflammatory process with prominent eosinophilia around ova or larvae (19).

Schistosomiasis is particularly prevalent in Africa and the Far East. *Schistosoma haematobium* and *S. japonica* mainly affect the genitourinary system while *S. mansoni* tends to involve bowel as well as other sites such as the central nervous system and geni-

tourinary system. The cercariae of S. *mansoni,* which emerge from snails, penetrate the skin to cause an itchy eruption in previously exposed individuals. About 8 weeks after infection Katayama fever with chills, pyrexia, sweating, headache, cough, hepatosplenomegaly and lymphadenopathy occurs. The worms may cause pseudotuberculous granulomas to develop in the liver but ova are mainly deposited in the colon and rectum. Complications from S. *mansoni* infection include: hepatic fibrosis leading to portal hypertension, and portal, mesenteric and vertebral vascular inflammation and fibrosis with subsequent involvement of the pulmonary vascular bed leading to cor pulmonale or neurological deficit and membrane-proliferative glomerulonephritis from circulating immune complexes (19).

Cestode infestations are less common in children than in young adults. The commonly occurring tapeworms are Taenia *soilum* (pork tapeworm) and the Echinococcus species. Cysticercosis due to *T sollum* affects diverse tissues but especially the brain, heart and muscles when autointection occurs from ova being passed in the feces. In *Echinococcus* infestation (hydatid disease) the embryos from ingested eggs very quickly pass through the gastrointestinal tract to the portal circulation to be filtered out in the liver, lungs and other sites where classical hydatid cysts containing larvae appear.

Infestation by the dwarf tapeworm *Hymenolepis nana* is commonly seen by microbiologists examining wet preparations of stool but the worms are rarely recognized by anatomical pathologists because of their small size. Heavy infestation may cause diarrhea and abdominal pain and constitutional symptoms associated with moderate eosinophilia. The cestode requires a single host but also infects mice, fleas and beetles (19).

References

1. Bishop WP, Ulshen MH. *Bacterial Gastroenteritis.* Pediatr Clin N Amer 1988; 35: 69-87.
2. Househam Kc, Mann MD, Bowie MD. *Enteropathogens associated with acute infantile diarrhoea in Cape Town.* S Atr Med J 1988; 73: 83-87.
3. Nachamkin I, Lastovica AJ. *Campylobacter Helicobacter and related organisms: Guillain-Barre Syndrome in Campylobacter, Helicobacter and related organisms.* In: Lastovica AJ, Newell OG, Lastovica EE. (Eds.). ICH University of Cape Town, cape Town 1998; 87-91.
5. Isaacson M, Hale MJ. Intestinal *bacterial intections.* In: Doerr W, Seifert G, Uchlinger E. (Eds.). Tropical Pathology. 2nd ed., Springer-Verlag, Berlin 1995; 157-177.
6. Cooke Gd. *Aetiology and pathogenesis of post infective tropical malabsorption (tropicalsprue).* Lancel 1984; 1: 721-723.
7. Buret A, Gall DG, Nation PN et al. *Intestinal protozoa and intestinal cell kinetics, structure and function.* Parasitol Today 1990; 6: 375-380.
8. Mills AE, Goldamid JM. *Intestinal protozoa in tropical pathology.* In: Doerr W, Seifert G, Uchlinger E. (Eds.). 2nd ed. Springer-Verlag, Berlin 1995; 477-556.
9. Mehlotra RK. *Entamoeba histolytica: From intestine to liver* Parasitol Today 1988; 4:235-236.
10. Luvuno FM, Mtshali Z, Baker LW. *Vascular occlusion in the pathogenesis 01 complicated amoebic colitis.* Br J Surg 1985; 72:123.
11. Mylins RE, Ten Saldam REJ. *Venerial infection by Entamoeba histolytica in a New Guinea Native couple.* Trop Geogr Med 1962; 14: 20.
12. Casemore DP, Armstrong M, Sands RL. *Laboratory diagnosis of cryptosporidiosis.* J Clin Path 1991; 44: 445-451.
13. Ali AA, Mahmoud LH, el-Zoheiry AA. *A study of intestinal helminths causing human anaemia in Cairo.* J Egypt Soc Parasitol 1989; 19: 251-256.
14. Chacin de Bonilla, Guanipa N, Cano G. *Fatal hypednfectious strongyloidiasis: Report of 3 cases.* Invest Clin 1990; 31: 61-82.
15. Rode H, Cullis 5, Millar A at al. *Abdominal Complications of Ascaris lumbricoides in children.* Pediatr Surg Int 1990; 51: 397-401.
16. Anstey L. *Granulomatous Ascaris hepatitis.* S Atr Med J 1966; 40: 13-15.
17. Days H, Allie A, McCarthy R. *Disseminated Ascariasis: A case report.* S Atr Med J 1982; 62: 820-822.
18. Taylor KL. *Ascariasis of the kidney* Pediatr Pathol 1995; 15: 609-615.
19. Marty AM, Andersen EM. *Helminthology in tropical pathology* In: Doerr W, Seifert G, Uehlinger E. (Eds.). 2nd ad. Springer-Verlag, Berlin 1995; 801 -982.

Examination of the placenta in late intrauterine death: What can we tell about cause and recurrence risk?

T. Stallmach

Dept. of Pathology, University Hospital Zurich, Switzerland.

During the past decades, there has been considerable advancement in the care of a fetus and its mother and, later on, of the newborn. With the great reduction of overall perinatal mortality in highly developed countries we have come to a stage where 50% of all perinatal losses are constituted by intrauterine death affecting a viable fetus older than 26 weeks of gestation. Severe fetal malformations are already excluded from this number, as are the few deaths that are caused by obvious bacterial or viral infections. Thus, the majority of fetal demise in the third trimenon is due to some kind of placental insufficiency that occurs in two quite different clinical settings and which can be described as "chronic" or "acute" placental insufficiency.

"Chronic" placental insufficiency

Chronic insufficiency comprises all conditions in which reduced placental function is reflected by fetal growth retardation. Obviously there are cases where the growth of a child for genetic reasons is below the 5th percentile and the placenta is small simply because the corresponding child is small. Growth retardation proper is characterized by a declining curve of fetal growth caused by *in* utero starving: it is thus necessarily "chronic". Starvation itself can be compatible with fetal survival for periods up to 6 and even 8 weeks. In general, compromise of the maternal circulation is better tolerated, especially when it occurs in "succession" as opposed to the compromise of fetal circulation, which is also much more ominous in regard to the underlying disease condition. *Post mortem* findings in the fetus will reveal severe reduction in the weight of internal organs, especially the liver, thymus and spleen with some growth parameters remaining around the 50th percentile for a long time, especially brain weight and foot length. The placenta of a growth-retarded child is usually characterized by areas that have ceased to function. These usually constitute gross morphological findings of a focal nature, the most typical being infarcts of different age, size and location. It is important to estimate the volume of placental tissue lost and to denote whether all infarcts have the same appearance (thus having occurred eventually all at the same time) or whether they exhibit different color and Consistency (giving the impression that they have occurred in succession). The most typical accompanying microscopic finding is an increased vascularization of the chorionic villi which have remained viable and which thus try to compensate for the losses. At the time when chronic placental insufficiency leads to fetal malnutrition, many of the mothers are also unhealthy; they have symptoms of preeclampsia, are