laparotomy or post mortem is found to be pigmented. Clinically, whereas patients with melanosis coli are constipated, those with lipofuscinosis usually have diarrhoea due to steatorrhoea. Malabsorption in these patients may be due to coeliac syndrome, chronic pancreatitis, fibrocystic disease of the pancreas, Whipple's disease, or jejunal diverticulosis. Lipofuscinosis is also seen in patients with hypoproteinaemia, usually due to protein-losing gastroenteropathy, and has been recorded in hepatic cirrhosis.[3] B. Fox[4] has recently described the features in three patients in whom pathological material was obtained at laparotomy and post mortem. Two of them had hypoproteinaemia. The pigment was deposited in large amounts in the smooth muscle of the small intestine, and was also found in blood vessels and macrophages of this organ. Post-mortem material from one patient showed lipofuscin in smooth muscle of the oesophagus and stomach, in the lymph nodes, various brain cells, hepatocytes and Kupffer cells of the liver, heart muscle, and in the Leydig cells of the testes.

Lipofuscins are a group of pigments formed by oxidation of cellular lipoids and lipoproteins. They have variable but characteristic staining properties, which, according to A. G. E. Pearse,[5] depend on the degree of oxidation and the type of lipid in the cell. Thus, although the histological appearance of lipofuscins may vary, they do seem to be a group of intimately related substances. In the liver lipofuscins are often known as ceroids, and are found in haemochromatosis, when they may form the organic matrix on which iron is deposited in the organ.[6] Brown atrophy of the heart, which occurs in a variety of terminal diseases, is due to lipofuscin in the cardiac muscle.

The intriguing question about lipofuscinosis is its cause. It may be due to vitamin-E deficiency, for animals fed diets deficient in this vitamin develop lipofuscinosis, as do some patients with vitamin-E deficiency and steatorrhoea.[7] Vitamin E is an antioxidant,[8] and it has been suggested that, when it is lacking, lipofuscins are formed by oxidation of cellular lipids. Other mechanisms involving mitochondria may be at work.[9] There is also a close association between vitamin E and protein metabolism, which may be a clue to the mechanism underlying the lipofuscinosis that is seen in patients with hypoproteinaemia.[10] As there is increasing evidence that vitamin-E deficiency occurs in various gastrointestinal disorders,[11 12] its role in producing deposition of lipofuscin in man needs to be fully investigated.

Lipofuscinosis does not have any specific clinical symptoms or physical signs, and there is no known treatment. Its cause and significance remain a challenge to the research worker, whether clinician, pathologist, or biochemist. Perhaps his efforts will be rewarded by a clear-cut answer, as was the case with melanosis coli and the anthracene purgatives almost forty years ago.

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Virus from Monkeys

Though fragmentary accounts of the disease acquired by laboratory workers in Germany and Yugoslavia from vervet monkeys have appeared, and the earlier laboratory findings been reviewed,[1] only now is a full clinical and epidemiological description of the disease available. G. A. Martini and colleagues[2] describe 23 cases which occurred in Marburg and W. Stille and colleagues[3] 6 cases in Frankfurt.

Estimates of the incubation period lie between four and nine days. There was a sudden onset of nausea, severe headache (mainly frontal or temporal), and tenderness of the eyeballs. During the first few days there was increasing fever, relative bradycardia, and pain and a feeling of tension in the trunk muscles and around the hips; vomiting was common. After one or two days there was often watery diarrhoea, with up to ten motions a day. As the fever subsided, from about the seventh day of illness, the vomiting decreased but the diarrhoea continued for several more days. In some patients there was a second febrile phase from the twelfth to the fourteenth days associated with myocarditis and orchitis. The severity of the diarrhoea in general paralleled the severity of the disease, though a few patients showed constipation, at least for a time. Dryness of the mouth was a common complaint, even before onset of diarrhoea and vomiting.

Between the fifth and seventh day of illness a rash appeared, most marked on the buttocks, trunk, and the outer aspects of the upper arms. At first there were red pinhead spots round the hair follicles; after about 24 hours the rash became maculopapular, then confluent. In severe cases there was a diffuse livid erythema on the face, trunk, and limbs, sometimes associated with cyanosis of the lips. Some cases had dermatitis of the scrotum or labia. In a few there were vesicles (on lips, abdomen, or thumb), some or all of which may have been due to recrudescent herpes simplex. After about the sixteenth day there was fine desquamation of the skin affected by the rash, especially on the palms, soles, forearms, and legs, lasting about two weeks. About half the patients had conjunctivitis at one time or another. There was also an enanthem which appeared a day before the rash in some patients—deep red discoloration and "sago-like" vesicles on the soft palate sometimes spreading to the hard palate. Some had inflamed tonsils with yellowish pinhead areas of exudate. Lymph nodes were small and not tender, but palpable, sometimes before the onset of the rash, in the neck and axilla. Two patients had signs of meningeal irritation, but the cerebrospinal fluid was essentially normal. Most patients were peevish and uncooperative at the height of the illness, but some had confusion, depression, or anxiety, and

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in some of the fatal cases restlessness and confusion were succeeded by coma and death. Some had loss of memory for the acute stage of the illness. There were also changes in peripheral sensation—hypersensitivity to pain and touch, "pins and needles," or a feeling of "lying on crumbs." Myelitis was recorded in one patient after the end of the acute stage of illness.

The patients developed a tendency to bleed, notably from the gums and from needle punctures. Haematemesis and melaena occurred, but the rash was never haemorrhagic. There was marked thrombocytopenia (less than 10,000 per cu. mm. in two fatal cases) but no other changes in blood-clotting factors sufficient to account for the bleeding. Transaminase levels (especially S.G.O.T.) were raised, and atypical lymphocytes and plasma cells were seen in association with leukopenia. Serum proteins (all components) declined in all cases, but significant proteinuria was not seen.

Seven patients died and the remainder had a slow convalescence. Three patients relapsed.[4] Of these, one had a marked rise in serum transaminase 31 days after recovery; the second had a similar rise 73 days after, associated with an acute psychosis, and the virus was isolated from a liver biopsy; the third appears to have infected his wife by sexual intercourse 11 weeks after recovery, and the virus was recovered from his semen.

The laboratory workers acquired infection from contact with monkey tissues or cultures from them, and not from contact with or care of the intact infected animals.[5] However, several cases were infected in hospital by contact with the blood of patients—a risk aggravated by their bleeding tendency. The agent was isolated from urine and throat washings of some patients as well as from blood.[4]

Necropsy examination indicated that necrotic changes had first affected the liver and lymphatic system, then the pancreas, gonads, adrenals, hypophysis, thyroid, kidneys, and skin. There was also evidence, supported by liver biopsy findings, that the liver damage was quickly repaired by regeneration after the acute stage. Basophilic bodies were seen in cells in and around necrotic lesions. In lymphoid tissue there was a notable transformation to plasma cells and monocyte-like cells. Similar cells had diffusely infiltrated the mucosa of stomach, small intestines, and less of the large intestine. All cases had severe parenchymal damage and evidence of tubular failure in the kidneys, associated with cerebral oedema. In patients who died in coma there was either some evidence of encephalitis (glial nodules) or a haemorrhagic state in the central nervous system.[7]

Some laboratory studies are also reported on the isolation of the virus in guinea-pigs and monkeys[8]; and serological studies, including fluorescent antibody work,[9] gave similar findings to those obtained at the Microbiological Research Establishment, Porton,[10 11] showing that the agent obtained there and in Germany is identical. Growth of the agent in human amnion cells is reported, and electronmicroscopy of it in blood gave a length of 800–1,000 mμ.[12 13]

The accumulated evidence shows that this is a previously unrecognized disease caused by an agent probably new to medical science. As the origin of the infection remains obscure, it would be unwise to assume that infections of man will not recur. Moreover they may come next time from another source, for vervet monkeys are clearly not the maintenance hosts of the virus. For instance, it is infective also for rhesus monkeys. The cases reported here were apparently due to contact with blood or tissues, but the presence of the agent in the throat and urine of both man and monkeys during the disease, and transmission of it by sexual intercourse, suggest that the epidemiological propensities of the infection may be wide. In any case of obscure febrile illness the attending doctor should always ensure that he has made inquiries about contact with wild or pet animals. Though the infection has not yet been found in monkeys in a latent or non-fatal form, the possibility cannot be dismissed that it will be either in them or in other species of animals in view of its persistence in man for up to 11 weeks after recovery. No specific treatment has been found for this disease.

Cystic Fibrosis and Fertility

More and more children with the autosomal recessive condition cystic fibrosis of the pancreas are surviving into adult life and eventually will be marrying. The genetic risks to their children are not high. Such survivors will transmit the gene to all their children, but the children cannot be homozygotes unless the other parent is also a carrier. In countries where the incidence of the disease is about 1 in 2,000 the carrier rate will be between 1 in 20 and 1 in 25 and the risk to children of those affected between 1 in 40 and 1 in 50. Detection of carriers is probably not too far away, and this will provide a further safeguard.

Girl survivors are known to be fertile; already at least 11 liveborn children have been reported and these children have all been unaffected.[1] So far, however, no surviving males have had children, and C. R. Denning, S. C. Sommers, and H. J. Quigley[2] have recently reported that 8 adult male patients with only mild pulmonary disease all had complete azoospermia. Not even any dead or malformed spermatozoa were found on careful search. The volume of semen was small and its turbidity was increased, but viscosity was normal and fructose was present. Testicular biopsy in one patient and necropsy of nine other male patients who died of cystic fibrosis showed spermatogenesis occurring and normal prostate and seminal vesicles.

The cause of the azoospermia is not established. The authors note that many spermatocytes were binucleate, or contained cytoplasmic inclusions or showed incomplete meiosis. They postulated some genetic abnormality of spermatogenesis. They also found low serum levels of vitamin A and vitamin E in the patients and suggested that this might be relevant. On the analogy of the pancreatic and salivary lesions the most probable mechanism of the azoospermia, however, is that there is a defect in transport of the spermatozoa owing to diminished water and electrolyte secretion.

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