described a patient who had a severe haemorrhagic state, in whom all conventional laboratory tests of clotting function were normal. They found that the patient's clots formed in plasma were soluble in 30% urea solution, and attributed the abnormality to deficiency of fibrin-stabilizing factor. Since then about 10 similar cases have been reported, a new one being added recently by A. Barry and J. M. Delâge,[4] while the first case in Britain has been described by M. S. Losowsky and his colleagues.[5] The haemorrhagic state in these patients is severe, with haemorrhage from the umbilical cord in the neonatal period, massive haematomata, cerebral haemorrhage, bleeding post-operatively and into joints, and delayed healing. The defect is probably inherited as an autosomal recessive trait, and Barry and Delâge found a slightly reduced level of fibrin-stabilizing factor in both parents of their patient. After transfusion the defect seems to be corrected for 6–14 days; thus for planned surgery an infusion of plasma should be an effective form of treatment, and for a patient with many episodes of spontaneous bleeding prophylaxis should be possible.

This is a very rare defect. It would not be reasonable to test the solubility of clots in urea as part of a routine screening procedure for haemorrhagic states, but for the occasional patient with severe bleeding whose blood gives normal results for other clotting tests there is now one additional simple test that may reveal the diagnosis.

Genetics of Intestinal Polyposis

The *Eugenics Laboratory Memoirs,* issued from time to time from the Galton Laboratory, University College, London, have come to occupy a place of special authority in the literature of hereditary diseases. The latest publication, on intestinal polyposis, has been compiled by Dr. A. M. O. Veale, who came from New Zealand to London a few years ago for the special purpose of undertaking research into the inheritance of this curious disease. He worked under the supervision of Professor L. S. Penrose, F.R.S., at the Galton Laboratory and of Dr. Cuthbert Dukes at St. Mark's Hospital, where he had the opportunity of studying the records of a large series of families in which one or more cases of intestinal polyposis had occurred. These records, which have been kept for more than 30 years, were the main source for the work now published.

Dr. Veale's special contribution is that he has reviewed the pathology and clinical aspects of each recorded case and then applied modern methods of genetical and linkage analysis. Application of these methods has added mathematical precision to conclusions arrived at by less sophisticated means. For a long time it has been known that there is a slight excess of cases of familial polyposis amongst males. Veale's analysis suggests that the difference is probably due to the sexes being unequally represented in the data rather than to sex linkage of genes. The occurrence of isolated cases without a family history can with confidence sometimes be attributed to fresh mutations, and a mutation rate of 13 per million gene loci per generation has been calculated for this disease. It is of about the same magnitude as mutation rates for other autosomal dominant diseases in man.[2] Failure to recognize the disease in previous generations explains the occurrence of some apparently isolated cases, and sometimes this failure is attributable to the fact that the disease, though present, does not manifest itself. Dukes[3] found that in families in which there had already been two or more cases of polyposis, and in which one parent carried the polyposis gene, only 40% of the children developed the manifest disease, indicating a manifestation rate, or penetrance, of 80%. This figure is almost exactly confirmed by Veale. Variation in the patient's age at the first appearance of polyps, start of symptoms, development of cancer, and death from cancer is wide, both between families and within them. According to Veale the data are consistent with the theory that a second "polyp-prone" gene, allelic with the polyposis gene, is involved. The inheritance of this second gene from the unaffected parent at the same time as the polyposis gene is obtained from the affected parent favours the early development of polyps, while the presence of the polyposis gene alone favours the late development of polyps. Inheritance of the polyp-prone gene with a normal gene (i.e., the heterozygous state) produces a condition indistinguishable from normal, but homozygosity with regard to the polyp-prone gene favours the development of isolated polyps, and thereby increases the chance of colonic or rectal cancer in persons not carrying the polyposis gene. This ingenious theory could help to explain the higher-than-expected incidence of cases of polyposis in which both parents appear to have had the disease.

Attempts to show linkage between the polyposis gene and other genes with recognizable bodily effects have given negative or equivocal results. The existing data suggest linkage between the Duffy (blood group) locus and the polyposis locus with a probability of 30%, but as more data accumulate this apparent association may disappear. Visible chromosomal abnormalities have not been detected in patients with polyposis, but characteristic particles have been found by electron microscopy in the cells lining the crypts of Lieberkühn.[4] Their nature is not yet known, but they are not found in normal people or patients with isolated polyps.

Veale's monograph on the genetics of intestinal polyposis constitutes, as Professor Penrose says in his introduction to it, "a remarkably complete description of a group of diseases which is of great interest, both from the point of view of human genetics and of cancer research." As such it is an excellent model for future investigations.

Rubella Virus and the Human Foetus

That rubella virus can injure the human foetus was first observed by N. McA. Gregg[1] after an outbreak of rubella in Australia. Early fears that the risk of foetal damage after maternal rubella might be very high have, happily, not been confirmed. Nevertheless, careful prospective studies have shown that the incidence of congenital abnormalities is considerably increased after rubella in early pregnancy. In a survey involving some 200 British children whose mothers had had rubella in the first trimester of pregnancy M. M. Manson, W. P. D. Logan, and R. M. Loy[2] found that the incidence of major congenital defects was 16% as compared with 2.3% in a control group of children. Similar results

[1] Veale, A. M. O., "Intestinal Polyposis." *Eugenics Laboratory Memoirs*, 1965, **40**. Cambridge University Press.
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[3] Dukes, C. E., *Ann. Eugen. (Lond.)*, 1952, **17**, 1.
[4] Birbeck, M. S. C., and Dukes, C. E., *Proc. roy. Soc. Med.*, 1963, **56**, 793.

were reported from Sweden, where R. Lundström[3] found that the incidence of major defects was 10% in 463 children who had been exposed to the risk of congenital rubella. Both surveys showed that maternal rubella in early pregnancy is also associated with an increased risk of spontaneous abortion, stillbirth, and prematurity.

Unfortunately it is now clear that the incidence of deafness is higher than originally thought. Late follow-up studies of both the British and Swedish children have shown that the number of cases of deafness increases as the children grow up.[4] Among the British children, for example, the incidence of deafness increased from a probable figure of 6% at 2 years to 19% when the children were between 3 and 5 years old.[2] When re-examined at 8 to 11 years of age further cases were discovered.[5] Fortunately the deafness is not always severe or bilateral, but only half the affected children in the British series were able to attend ordinary school. In Sweden the incidence of it at late follow-up was 22%[6]. Long-term follow-up failed to reveal any previously undetected cases of major defects, but in Britain eight children with defective vision were discovered at the re-examination between 8 and 11 years of age. These facts emphasize the need to re-examine at intervals throughout childhood all children born to mothers who have had rubella in early pregnancy. The examination should be directed particularly towards detection of loss of hearing, but should include tests of vision also.

At page 1027 of this issue Professor N. R. Butler and his colleagues report the results of a study which further confirm the need for this. Detailed auditory and ophthalmic tests were carried out at the age of 1 to 3 years on 70 children who had no obvious defects at birth and whose mothers developed rubella in early pregnancy despite the administration of gamma-globulin.[7] This revealed 12 cases of deafness —2 of which had not previously been suspected—and 16 patients with pigmentary retinopathy, 8 of whom also suffered from loss of hearing. Pigmentary retinopathy is common after congenital rubella and indicates that the eye was infected with the virus. Fortunately it does not seem to be associated with any visual disturbance. Serological studies on these children proved to be of considerable interest. It is known that infants with rubella syndrome are "immunologically competent" and produce antibody to the virus,[8 9] and this study confirmed that nearly all (90%) of the children found to have defects possessed rubella antibody. However, there was also serological evidence of infection in 42% of the 50 children without defects. In contrast, rubella antibody was present in the sera of only 5.6% of 36 children who formed a control group. This shows that rubella virus can infect the human foetus without causing apparent injury. Just as in older children rubella infection is often symptomless,[10] so it seems that infection of the much more susceptible foetal tissues can also be silent.

Although little is known of the way in which rubella virus attacks foetal tissue, virological techniques[11 12] developed in the last three years have already provided some information. Post-mortem examinations of infants with rubella syndrome have shown that the virus is widespread in the organs and tissues.[13] It can also be isolated from a variety of sites in surviving infants—both in those with rubella defects and in apparently healthy infants born to mothers who had rubella in early pregnancy. These sites include the throat, rectum, urine, cerebrospinal fluid, blood, and bone-marrow. In a virological investigation of infants born after an outbreak of rubella in Texas[14] virus was isolated from 20% of 321 specimens taken from 85 infants in the first month of life. In the second month the isolation rate fell to 7%, but during the third month and up to 100 days of life 14% of 126 specimens yielded rubella virus. The fact that virus was found in one-third of 54 specimens of cerebrospinal fluid was particularly striking and indicates that this fluid should be examined for it in addition to the more usual swabs from the throat and specimens of urine. These results are of great interest because they show that rubella virus persists in the tissues of infected but apparently normal infants. They also suggest that virological tests carried out on infants who have been exposed to the risk of congenital rubella may be of practical importance. The finding of rubella antibody or the isolation of rubella virus, for example, may indicate that a child has a greater risk of developing a defect such as loss of hearing or defective vision. The earliest possible detection of these defects is essential if they are to be adequately dealt with and the children given the best chance of normal education.

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Health in the New Towns

Though the plea is often heard for more experiment in the type of premises used by general practitioners, this kind of change can be difficult to make in established practices. The new towns, however, are an obvious field for experiment, and several of the development corporations have included in their plans schemes co-ordinating the medical and social services in common premises. A new town still at the drawing-board stage is the riverside one at Woolwich and Erith in south-east London, and the General Practice Research Unit at Guy's Hospital Medical School has been concerned in helping to plan the health services there. Some of their proposals were discussed with development managers from the new towns and doctors at a meeting on 15 October. The research was made possible by a generous grant of £36,000 over five years from the Nuffield Foundation.

Speakers at the conference differed about the best method of organizing health services. Some suggested that the changing pattern of general practice, with its increasing emphasis on preventive medicine—and thus on screening procedures—has made any attempt to provide the patient with a doctor and welfare services all within easy walking distance of his home quite unrealistic. They argued that the collection of all the community services into one building has advantages beyond the economic ones of centralization. For example, this kind of clinic makes it easier for doctors to establish a good working relationship with those in the social services, and gives close contact with medical colleagues. On the other hand, Lord Taylor pointed out