The present cases indicate that, since the multiple painless lesions are of the vascular type, this correlation is probably significant. However, there is no explanation why a solitary cellular painful malformation should occur in one person while multiple vascular painless lesions appear in another. It is probable that two quite different factors are operating to produce these two groups of cases. The solitary cellular lesion represents an isolated malformation occurring sporadically and quite accidental in origin. The multiple vascular telangiectatic type of anomaly may be genetic in nature as suggested in this instance, where brother and sister are similarly affected; and they described an identical lesion on their late father. The diffuseness of the distribution of these telangiectatic lesions favours the probability of such a general somatic factor being responsible. The progressive appearance over several years is still consistent with our knowledge of glomus-cell production, this being normally a post-natal development, and may in fact occur anywhere from aggregation and hyperplasia of local spindle cells normally in and around any blood-vessel walls. The possible initiation of some lesions by local trauma is suggested in the history of both cases reported, and it may be significant that each injury involved a puncture wound, by needles and once by a nail.

Thus it seems that the basic abnormality in these patients is vascular, the occurrence of telangiectases being distinguished by a hyperplasia of glomus-type cells irregularly scattered in the walls. It is suggested that such multiple painless lesions can be separated from the solitary lesion, wherein cellular proliferation is more prominent, and that nearer-to-normal glomus structure is reproduced both structurally and functionally.

Summary

Glomus-cell development is a normal postnatal event, and abnormalities of this process may result in a range of lesions showing different degrees of glomus-cell hyperplasia and different proportions of vascular to cellular components in these lesions.

While the usually solitary cellular painful glomus "tumour" or hamartoma is well recognized, the multiple, more vascular or telangiectatic type of painless lesions is not.

Two cases, those of a brother and sister, are reported with multiple painless glomus lesions, and the significance of these lesions is discussed in relation to the present concepts of glomus-cell abnormalities.

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A booklet, *Notes on W.V.S. Health and Hospital Work*, gives a bird's-eye view of the work done by the Women's Voluntary Services in hospitals (canteen work, shopping, library services, work in out-patient departments, and staffing telephone trolleys), in the blood transfusion, mass radiography, and hospital car services, and in their work for sick and handicapped people in the community. There is a list of useful books and an index. Inquiries should be sent to W.V.S. Headquarters, 41 Tothill Street, London S.W.1.

SYNDROME OF COLOBOMA WITH MULTIPLE CONGENITAL ABNORMALITIES IN INFANCY

BY

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During the past ten years coloboma of the eyes has been noted in four infants in our paediatric wards, and in every case it has been accompanied by other congenital abnormalities, particularly affecting the brain and heart. The main features of these cases are here described.

Case 1

A male infant was admitted to the Warrington General Hospital when 12 days old, with a history of increasing jaundice since birth, slowness in taking feeds, and general weakness. He had been born at home, a forceps delivery complicated by intrapartum haemorrhage. The birth weight was 7 lb. 8 oz. (3,400 g.). The mother's pregnancy was normal. There are two other children, both normal.

On admission he was jaundiced and a large cystic mass could be palpated, filling the lower part of the abdomen. Bilateral colobomata in the "typical" position were noted, involving the choroid, retina, and iris of both eyes. A systolic murmur could be heard to the left of the sternum. He had to be tube-fed. He was transferred to the neonatal surgical unit at Alder Hey Children's Hospital, where an intravenous pyelogram showed a normal right kidney but no excretion of dye on the left side. Laparotomy revealed the presence of an enormous hydronephrosis on the left side, compressing the inferior vena cava and the common bile-duct, this being the cause of the jaundice. Nephrectomy was performed and the jaundice gradually faded. It soon became evident that he had a severe degree of cerebral palsy. Head control and sitting were much delayed; both arms were spastic and his legs were small, weak, and hypotonic.

At the time of writing, aged 5 years, he could not assume the sitting position unaided, nor could he maintain his weight on his legs for more than a few seconds. He was speechless and his comprehension was almost negligible. He was able to see objects which were close to him, but vision was poor and there were constant searching movements of his eyes. He could pick up large objects but dropped them immediately. His head circumference was only 18½ in. (47.5 cm.). The cerebrospinal fluid was normal. Cardiac enlargement was present with cyanosis of the lips, fingers, and toes. There was a systolic thrill and murmur, maximal in the second left intercostal space. The E.C.G. showed right ventricular dominance and x-ray examination and cardioscopy showed right ventricular enlargement, concave pulmonary arc, and diminution of pulmonary vascular markings, these findings being indicative of pulmonary stenosis. He had difficulty in swallowing solid food and severe nutritional anaemia occurred on two occasions. Respiratory infections occurred and also large faecal accumulations in the rectum. His scrotum was cleft—this, together with a small penis, giving an almost hermaphrodite appearance.

Case 2

This patient was born in June, 1955, at the Warrington General Hospital, a full-term normal delivery, his birth weight being 8 lb. 15 oz. (4,055 g.). The pregnancy had been normal and there was one other child, aged 3 years, in good health. A number of congenital abnormalities were noted after birth, including talipes equinovarus of the left

foot and right inguinal hernia. There was a small fatty pad over the lower lumbar region of the spine, and radiographs of the spine showed a hemivertebra at the lumbosacral junction. "Typical" colobomata of both eyes involved the choroid, retina, and iris. Searching nystagmoid movements of the eyes denoted defective vision. His urine was normal on laboratory examination and his blood urea was 64 mg./100 ml. In view of the renal abnormality found in the previous case an intravenous pyelogram was done, but this was normal.

His head began to enlarge rapidly. His head circumference at birth was 14 in. (35.5 cm.), by the age of 3 weeks it was 15½ in. (39.4 cm.), and at 2 months had reached 16½ in. (42 cm.). Lumbar air cephalography showed a large amount of subarachnoid air and some dilatation of the ventricles. Feeding was always difficult. The legs became spastic, particularly on the right side, and there were bilateral extensor spasms. His arms were spastic and his hands remained clenched. He could hold objects but made no attempt to grasp. At the age of 1 year he was unable to sit up and comprehension seemed almost absent.

Soon after birth a loud systolic murmur could be heard to the left of the sternum. His heart enlarged, he was dyspnoeic at rest, and there was marked lower-rib recession. The apex beat extended out to the anterior axillary line and there was heaving of the right ventricular outflow tract. The pulmonary second sound was accentuated and split. A loud systolic murmur was heard, maximal at the end of the third left intercostal space, and there was a low-pitched diastolic murmur at the apex. X-ray examination and cardioscopy showed an enlarged pulmonary arc with left ventricular enlargement and increased hilar and pulmonary vascularity. In the E.C.G. there was an R wave with an upright T wave, suggesting left ventricular diastolic overload. These findings pointed to a diagnosis of persistent ductus arteriosus. He suffered from recurrent respiratory infections and died from pneumonia in October, 1956.

Case 3

This infant was born in November, 1959, at a Warrington maternity home, a normal delivery, her birth weight being 4 lb. 10 oz. (2,100 g.). Her mother had had a lobectomy in 1950 for bronchiectasis, but the pregnancy was uneventful. The infant had an abnormal facial appearance with wide-set prominent eyes, strabismus, and some beaking of the nose, superficially resembling Crouzon's disease. A small cleft was present in the posterior part of the soft palate. Coloboma was present in the left eye in the line of the foetal fissure, affecting the iris and the marginal part of the lens in the 7 o'clock meridian. There was some thinning of the choroid and retina, possibly representing a minimal degree of coloboma.

A loud systolic murmur could be heard to the left of the sternum, and subsequent cardiac investigation revealed the following signs: no dyspnoea or cyanosis at rest; slight upper sternal prominence; weak pulmonary second sound; and grade 4 high-pitched systolic murmur without a thrill, maximal in the second left interspace. A phonocardiogram showed an ejection-type systolic murmur with variable splitting of the pulmonary second sound and low amplitude of the second element. X-ray examination showed moderate cardiac enlargement involving the right ventricle, with full pulmonary arc and pulmonary oligoemia. A diagnosis of pulmonary stenosis was later confirmed by cardiac catheterization. Cyanosis and clubbing of the fingers have since developed.

The infant has failed to grow, her weight at the age of 9 months being only 8 lb. 9 oz. (3,885 g.). A radiograph of her wrist does not yet show any carpal centres. She is unable to sit up or even hold her head erect when lifted up. Her legs tend to remain in the foetal position and a persistent grasp reflex is present in the hands and feet. The knee- and ankle-jerks in the right leg are exaggerated and

her right hand tends to remain clenched. She cannot hold objects in her hands and she does not observe her surroundings with much sign of comprehension. The head circumference is only 15½ in. (39.4 cm.), the x-ray picture of the skull being normal. There has obviously been a serious failure of brain development. The infant's urine was shown to be normal apart from a slight trace of albumin, and a hyalase pyelogram did not reveal any developmental abnormality of the kidneys.

Case 4

This patient was born at home in July, 1960. During labour some bleeding occurred per vaginam, which prompted the midwife to make a vaginal examination. A soft mass was palpable, associated with some further bleeding, and it was thought to be a placenta praevia. In actual fact a large meningo-encephalocele was presenting, and it had partially ruptured. The mother, who used to suffer from epilepsy, had not been ill during the pregnancy, although she had fallen downstairs at the fifth week without injuring herself. There is one other child aged 4 years, and she is quite healthy. The birth weight was 6 lb. (2,720 g.).

The infant was admitted to the Warrington General Hospital a few hours after birth. His head looked small, and projecting from a midline hiatus in the region of the posterior fontanelle was a large red mass of cerebral meninges which also contained some brain tissue. The encephalocele seemed acutely tender and if lightly touched made the infant cry. The other major abnormality was bilateral colobomata in the line of the foetal cleft, involving the choroid, retina, and iris of each eye. Surprisingly enough, the infant thrived, taking feeds hungrily, his colour was good, and the limb tone was normal without evidence of weakness. He was transferred to the neonatal surgical unit at Alder Hey Children's Hospital. The sac, which had become infected, was excised together with some infected brain tissue, the meninges were sutured, and the skin was sutured over the deficiency in the skull.

The infant at the time of writing was 11 weeks old and had continued to make good progress. The head looked a little dolichocephalic due to the bulging of the scalp over the occipital foramen. There was ability to see, as he seemed to take notice of his surroundings. He held his head erect and made some attempt to hold objects placed in his hands. In this case there was no evidence of cardiac or renal disease.

Discussion

The eyes of all four children were affected by "typical" colobomata, this term implying that the coloboma occurs in the line of the foetal fissure. In three of the cases the colobomata were bilateral, involving the choroid, retina, and iris, the remaining case having a unilateral coloboma of the iris and lens with minimal changes in the retina and choroid. The most widely held theory of causation of coloboma of the choroid is that it is due to an ectodermal epiblastic hyperplasia of the lips of the foetal fissure, with excessive growth of the inner retinal layer leading to its eversion. If there is a coincident coloboma of the iris the aetiology is identical, as there is then a deficiency of the rim of the optic cup in the line of the foetal cleft (Mann, 1937).

Each of the children described has suffered a serious error of brain development, and three of them also have grave congenital heart disease. It is interesting to note that pulmonary stenosis was present in two of the three cardiac cases. The other major abnormality occurring in one of the children was congenital hydronephrosis. None of these congenital abnormalities are particularly

uncommon *per se*, but it is apparent that children with typical colobomata of the choroid, retina, and iris are liable to have multiple congenital abnormalities, particularly affecting the brain and heart.

The aetiology of congenital developmental anomalies still remains obscure. In none of these families was there any history of hereditary or familial incidence of coloboma or any other congenital abnormality. A genetic theory of causation therefore is not likely but certainly cannot be ruled out. Various infections of the mother during pregnancy may cause developmental errors. It is well known that rubella infection during the early months of pregnancy can cause cataract, congenital heart disease, deafness, and mental retardation. In none of these cases was there any history of infection, although a virus infection during pregnancy could pass unnoticed. There is a widely held theory that the same agent can produce different types of deformity, depending on the stage of development of the embryo during which it acts. Its action is most marked on structures which are actively differentiating. Soon after gastrulation the neural tube, optic vesicle, and the heart are in an active state of differentiation, all at the same time, and are all at the anterior apical end of the embryo. It might be expected, therefore, that an adverse environment between the first and second months of pregnancy could produce coincident damage to the eye, brain, and heart. Even at this stage the metanephric duct and palatine shelves are present but possibly not actively differentiating, as congenital hydronephrosis and cleft-palate were not a constant feature in all the cases.

There are not many references in recent literature to similar cases, but Rolando and Jemma (1959) have recorded one such case of a girl aged 7 years with bilateral "typical" colobomata of the choroid, retina, and iris, who had congenital heart disease due to a patent interventricular septum; also a congenital kidney defect with a double renal pelvis and ureter on one side and a pelvic kidney with short ureter on the other. The child's mother had contracted virus hepatitis early in pregnancy, and it was thought that this might have been the causative agent. It is possible that detailed investigation of cases similar to those described might prove of value in establishing the aetiology of congenital developmental abnormalities in the human embryo. Preliminary investigations point to some chromosome abnormality in Case 1.

Summary

A syndrome is described of congenital colobomata associated with other congenital developmental errors, particularly of the brain and heart.

Details are given of four cases, with some discussion of aetiology.

I thank Professor John D. Hay and Dr. Olive Scott for cardiac investigations at the congenital heart department of the Royal Liverpool Children's Hospital; Mr. P. P. Rickham and Mr. J. H. Johnston for surgical investigation and treatment at the neonatal surgical unit at Alder Hey Children's Hospital; and Mr. A. V. Clemmey for ophthalmic investigations and reports.

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Medical Memoranda

Polycythaemia and Renal Carcinoma

In recent years the coexistence of polycythaemia with renal carcinoma has been reported in a number of cases, and it seems likely that some 4% of patients with renal carcinoma may show polycythaemia. The majority have been recognized in retrospect, although the polycythaemia may be the presenting symptom. Although the mechanism is not established, overaction of erythropoietic principle may be considered.

CASE REPORT

A woman of 73 living in the Yorkshire Wolds had for a year complained of redness of the face and headache. In May, 1958, painless haematuria began. On admission 10 days later she showed a good normal colour. There were no palpable abdominal swellings, and, apart from a doubtful low-grade pyrexia, no other clinical abnormalities. The urine contained a moderate amount of blood, a little pus, and a growth of *E. coli*. The blood urea was 37 mg./100 ml. As shown in Table I, she had a moderate polycythaemia.

TABLE I.—*Haematological Findings*

	Hb %*	R.B.C. Millions	Haemato- crit (%)	Retic. %	W.B.C.	Platelets
May 23	133	6.6	65			
" 27	136	—	—			
" 29	130	6.5	63	1.0		120,000
" 30	133					
" 30			Nephrectomy			
" 30	104					
" 31	101					
June 7	96				5,000	
July 16	96				6,000	
Jan. 30	108	4.7	45	<1	7,000	
May 5	118	5.7	50	<1	7,000	
June 6	109	5.3	45	<1	5,000	
" 26	103	4.7	44	<1	6,000	

* Estimated by the M.R.C. Grey Wedge photometer. (100% = 14.8 g.)

Cystoscope, pyelograph, and straight abdominal x-ray film indicated a right renal growth. On May 30—that is, 18 days from onset of symptoms—nephrectomy was performed, and a tumour of the upper pole of the kidney was confirmed. No enlargement of the spleen or other abnormality was observed. Recovery was comparatively uneventful, and she has remained well during the subsequent year.

The haemoglobin fell to normal within a few hours after operation, and has remained so during the subsequent year.

The Tumour.—The right kidney had, replacing the upper pole, a moderate-sized round mass, lumpy, and of varied colour. Blood-vessels were not especially prominent in the capsule. The cut surface was a variegated red, yellow, or translucent—in fact, it was a typical renal carcinoma. Microscopically the appearance was of a well-differentiated clear cell growth. A number of blocks from different areas had a similar appearance. The adjacent kidney showed no unusual feature.

Previous cases of renal carcinoma recorded in this hospital group over the last 10 years were listed. In none of the 15 on record was there polycythaemia. The sections were examined and compared with the present case. The stains used were haematoxylin and eosin, Masson's trichrome, periodic acid Schiff, and aldehyde fuchsin. A proportion were of clear cell type, similar to the present case, and no feature distinguishing this case could be found.

COMMENT

The diagnosis of renal carcinoma accompanied by polycythaemia has been reported in 38 cases (Table II). The growth has in most reports been confirmed by microscopy. Where described, this is mostly given as