Papers and Originals

Some Unusual Developmental Heterotopias*

R. A. WILLIS,† M.D., D.SC., F.R.C.P., F.R.A.C.P., F.R.C.S.

[WITH SPECIAL PLATE BETWEEN PAGES 268 AND 269]

Brit. med. J., 1968, **3**, 267-272

I feel it to be a special privilege, and a special responsibility, to give a Roy Cameron Lecture, for he was my very dear friend. It is just over 50 years since he and I entered the medical course together at the University of Melbourne in 1917; and during the passage of those years our friendship grew increasingly deeper and more valued by us both. For another reason also I feel a peculiar responsibility in undertaking this lecture—namely, that, while Roy Cameron excelled as a great experimental pathologist and a great teacher of the dynamic aspect of pathological research, most of my own work has been in the more conventional fields of structural pathology. However, I took heart when I recalled that two of Roy's earlier teachers, whom he greatly venerated, Sir Harry Allen and Ludwig Aschoff, were morbid anatomists, and that Roy himself, though pre-eminent as an experimentalist, was also an experienced histopathologist. Indeed, in a letter to me in 1963, concerning an important committee meeting which he had just attended, at which the training of young pathologists was discussed, he wrote: "I spoke very strongly about the importance of a sound training in morbid anatomy and histology for the experimentalist. Some people apparently forget that I went through a long apprenticeship myself and was responsible for most of the routine biopsy and necropsy work at U.C.H. until a very few years ago."

For the foregoing reasons I decided that a purely morphological subject, besides being within my own province, would not be an inappropriate one for this lecture. But I wanted it also to be one with a strong functional or dynamic interest—one in which the structural abnormalities studied impel us to reflect on their functional implications or on the basic biological processes that engendered them or on which they may shed light.

Such topics are plentiful in structural pathology. I might, for example, have chosen to speak on the *regeneration* of lost or damaged tissues, a very wide subject, the morphological and functional aspects of which are barely separable, and one which particularly engaged Roy Cameron's attention. Or I might have spoken on *metaplasia*, the divergent differentiation of proliferating adult tissues, one familiar instance of which—bony metaplasia in soft tissues—excited Roy Cameron's special interest. Or I might have reviewed the contribution of the histopathology of tumours to our knowledge of the functions of the *endocrine secretions*, and of the still little understood secretion of hormones or hormone-like substances by tumours of non-endocrine tissues, especially bronchial carcinoma.

I have chosen, however, to speak on the subject of developmental heterotopias, mainly because of some correspondence that I had with Roy Cameron in 1957. He wrote to me: "I am trying to get my ideas clear about the subject of hetero-

topia, especially of stomach, thyroid, adrenal, etc. I cannot put my hand on any useful review or paper. Could you give me a few references?" It happened that just at that time I was myself reviewing the literature and my own collected material on this subject for the chapter in my projected book, *The Borderland of Embryology and Pathology*, and I sent Roy a copy of my script, along with a selection of references and a few unusual specimens. In his reply he said: "I enjoyed the chapter very much. . . . It raises all sorts of questions in my mind. You can well imagine that I was particularly interested to read of any cases in which heterotopias functioned as compensatory mechanisms. . . . I knew how ignorant I have always been on congenital abnormalities as a whole, but I didn't know how many fascinating things I was missing."

In the ten years that have passed since that correspondence I have had the opportunity, through the kindness of many fellow pathologists, of studying many more instances of developmental heterotopias—some of them so unusual that I am sure they would have greatly excited Roy Cameron's interest—and I propose to make these the subject of my talk. In selecting them I have purposely chosen examples of heterotopic alimentary, pancreatic, and hepatic tissue, because a large part of his research work concerned these tissues.

Before describing the specimens, however, I must clarify the meanings of two words that I shall frequently use, *heterotopia* and *heteroplasia*. *Heterotopia* is the more general term, embracing all kinds of ectopic or misplaced tissues, whatever their mode of genesis. This may take place in at least three different ways—namely, (1) by abnormal persistence and development of vestigial structures (for example, the development of an accessory lingual thyroid from the upper end of the thyroglossal duct); (2) by the dislocation of part of a definitive organ rudiment during the mass movements of developing tissues—for example, the downward carriage of adrenal or splenic rudiments during the descent of the gonads, forming small accessory nodules of adrenal cortex in retroperitoneal or juxtagonadal positions or an intrascrotal spleen; and (3) by *heteroplasia*—that is, the abnormal differentiation of the local tissues because of their peculiar situations in malformations, the most familiar example being the differentiation of gastric mucosa instead of the expected intestinal mucosa, and sometimes also pancreatic tissue, in a Meckel's diverticulum. The gastric and pancreatic tissues here are not derived from dislocated rudiments of the gastric and pancreatic primordia, but are the product of a primary anomaly of differentiation of the plastic mid-gut endoderm in the diverticulum during its embryonic development—that is, a heteroplasia. Such heteroplastic anomalies of differentiation are frequent in many kinds of malformations, especially those of the alimentary canal, and most of the specimens which I am about to describe exemplify this. I shall describe the specimens regionally, beginning with those of the head and neck.

* The Roy Cameron Lecture delivered before the College of Pathologists on 8 May 1968.

† Emeritus Professor of Pathology, University of Leeds.

Heterotopic Tissues in Head and Neck

Heterotopic tissues in the head and neck are most often seen in persistent vestigial structures, especially the branchial and thyroglossal vestiges. In many cases the epithelial components of cysts or sinuses arising from these vestiges are of ordinary kinds conforming with those of their region of origin. But occasionally tissues of unexpected kinds are present in facial or cervical malformations, as in the following five examples.

Case 1

R 2073 ; by courtesy of Dr. R. C. Hadley and Dr. B. H. Landing, Los Angeles, California.

At birth a male infant had a skin-covered firm protrusion in the right supraorbital region (Fig. 1, Special Plate). Radiographs showed the base of this to contain an excrescence of the frontal bone, but the inner table of the bone was normal. The bulk of the mass was excised and the bone surface was trimmed; the child remained well eight years later. Microscopically, beneath the skin the mass consists of a single well-developed unerupted tooth set in a socket of alveolar bone. In view of the possibility that the lesion might be teratomatous, sections were cut at several different planes, but no other heterotopic tissues were found; and the conclusion was reached that it was indeed only a misplaced tooth, socketed in the frontal bone.

Comment.—Nasal, facial, and mastoid teeth have been reported, but none as far from the definitive dental-shelf region as this one. We can only speculate about its exact histogenesis. Either a part of the dental shelf proper got carried into the abnormal position during the complicated growth movements of the several embryonic outgrowths that coalesce to form the face; or, more likely I think, a fragment of undifferentiated and non-specific ectoderm, sequestered by these movements—just as happens in the formation of the well-known congenital dermoid cysts about the face—underwent heteroplastic dental differentiation, and the resulting tooth induced the subjacent frontal bone to provide it with a bony socket.

Case 2

R 3998 ; by courtesy of Dr. J. D. Bradley-Watson, of Luton.

A girl of 15 had only recently noticed a swelling in her neck; clinically and at operation this was regarded as a branchial cyst. The excised specimen was a well-defined ovoid mass 6 cm. in main diameter, which on section showed a large thick-walled cyst in its upper part and many small loculi with mucoid or creamy contents in its lower part. Microscopically, parts of the cystic spaces are lined by stratified epithelium with deep crypts extending into an underlying zone of lymphoid tissue—a tonsil-like relationship often seen in branchial cysts. Of more interest is the presence in the outer parts of the cyst walls of plentiful lobules of well-differentiated thymic tissue with Hassall's corpuscles, and a small parathyroid gland.

Comment.—In view of the pharyngeal nature of the epithelium lining many deep-seated branchial cysts, it is not surprising that they should sometimes develop accessory thymic or parathyroid tissue in their walls, though indeed these have seldom been recorded. In the present case the development of both of these unusual components may be taken as strong evidence that the cyst arose from vestiges of the third internal pharyngeal pouch, for it is from this pouch that both the thymus and parathyroid normally arise.

Case 3

T.R.C. 575 ; by courtesy of Dr. G. R. Osborn, of Derby (see Willis, 1962b, Fig. 41).

A girl 19 months old, who had been coughing and vomiting for one week, was found to have a polypoid mass arising by a narrow pedicle from the posterolateral wall of the nasopharynx. This was

removed, with permanent relief. It was nearly cylindrical, 3 cm. long and 5 mm. in diameter, with some small lobular excrescences. Microscopically, a squamous stratified epithelium without skin appendages clothes a core of cartilage, connective and adipose tissues, and mucous and mixed glands; and one of the side lobules contains a small parathyroid gland.

Comment.—I have examined several similar simple epignathi, composed exclusively of components derivable from the local tissues, and devoid of exotic tissues such as we might expect if the growths were teratomatous. Like most other pathologists, I have hitherto supposed all epignathi to be teratomas, but I now believe that there are two distinct kinds of them—a rare kind which is truly teratomatous and related to the rare teratomas of the base of the skull, and a less rare kind which are local malformations involving only the tissues of the region. Some of these tissues, however, like the parathyroid nodule in the present case, may be heterotopic, either by dislocation of a predetermined rudiment or by heteroplastic differentiation.

Case 4

R 4142 ; by courtesy of Dr. M. Fowler, of Adelaide, South Australia.

The mother of a baby boy 4 months old had noticed a swelling in his tongue since he was 6 weeks old. It was situated on the right border of the tongue at the junction of the anterior two-thirds and posterior third. At operation it was found to be well defined, about 1 cm. in diameter and cystic, and during removal it ruptured and discharged mucoid fluid. Microscopically (Fig. 2, Special Plate) the cyst is lined by intestinal mucosa with crypts with Paneth and argentaffin cells, as well as goblet cells. This is surrounded by a well-developed, two-layered muscle coat, outside which a zone of fibrous tissue demarcates it from the lingual muscle.

Comment.—Elsewhere (Willis, 1962a, pp. 292 and 326) I have mentioned another cyst in an infant's tongue, which was lined by gastric mucosa, and have referred to a case reported by Schultz (1927), in which a congenital cystic lesion in the floor of the mouth also probably contained gastric tissue. These cases and the one just described can be explained only by the assumption that sequestered pieces of endoderm at the extreme anterior end of the primitive foregut—possibly vestiges of the thyroglossal duct—are capable of heteroplasia to form tissues appropriate to much more caudal levels of the gut. This is shown even more strikingly in the next specimen.

Case 5

R 4077 ; by courtesy of Dr. F. J. Glassy, of Sacramento, California.

A well-circumscribed congenital mass 4.5 by 3 by 2 cm. was removed from the soft tissues in the left zygomatic region of a baby boy when he was 3 weeks old. The mass comprised several cavities with mucoid contents and intervening areas of solid tissue. Microscopically, the cavities are lined by mucosa of varying structure, much of it gastric or intestinal, but with some small interspersed areas of stratified oesophagus-like epithelium, and one area of pseudostratified ciliated epithelium of respiratory type. Plentiful smooth muscle surrounds the gastrointestinal cavities, and appropriately situated in relation to this are nerves and nerve ganglia. The solid tissues intervening between the cavities comprise plentiful well-differentiated pancreatic tissue, and one piece of liver, 8 mm. in main diameter, in which some haemopoiesis is in progress (Fig. 3, Special Plate). Except for some lobules of foetal adipose tissue and some small haemolymph nodes, these are all the tissues that are present.

Comment.—In this malformation we have an unusual variety of well-differentiated foregut derivatives, and, apart from appropriate muscular, nervous, and adventitial tissues accompanying them, only foregut derivatives. For this reason, and also because of its situation, the lesion is almost certainly not teratomatous, but must be ascribed to widely divergent heteroplasia in a piece of foregut endoderm, dislocated during the

R. A. WILLIS: SOME UNUSUAL DEVELOPMENTAL HETEROTOPIAS

FIG. 1.—Case 1. Supraorbital protrusion due to an unerupted tooth.

FIG. 2.—Case 4. Lingual cyst lined by intestinal mucosa. ($\times 70$.)

FIG. 3.—Case 5. Pancreas (above) and liver (below) in facial mass. ($\times 70$.)

FIG. 4.—Case 6. Pancreatic tissue, along with thymus, in wall of anterior mediastinal bronchogenic cyst. ($\times 70$.)

FIG. 5.—Case 8. Epithelial inclusions in heart. ($\times 70$.)

FIG. 6.—Case 9. Whole section in long axis of jejunal diverticulum, showing its mucosa, thick two-layered muscularis, and an encircling muscular band SS. ($\times 4.6$.)

R. A. WILLIS: SOME UNUSUAL DEVELOPMENTAL HETEROTOPIAS

FIG. 7.—Case 9. Mucosa of diverticulum lined by desquamating squamous stratified epithelium, with prominent ducts traversing muscularis mucosae, and glands in submucosa. ($\times 70$.)

FIG. 8.—Case 9. Cross-striated muscle of band SS of Fig. 6. ($\times 500$.)

FIG. 9.—Case 10. Gastric mucosa in malformation of bladder. ($\times 70$.)

FIG. 10.—Case 11. Haemangiomatous tissue. ($\times 70$.)

FIG. 11.—Case 11. Foetal liver tissue with plentiful haemopoiesis. ($\times 70$.)

FIG. 12.—Case 11. Enlarged view of Fig. 11. ($\times 290$.)

complex movements of facial development. I have been unable to find any previous report of heterotopic pancreas and liver in the facial region.

Heterotopic Tissues in Thorax

Heterotopic tissues in the thorax occur in malformations of at least three different sources—namely, (1) cervical structures that have been carried too far caudally, as in the well-known mediastinal thyroid and parathyroid glands; (2) malformed or sequestered parts of the respiratory system, often forming bronchogenic cysts; and (3) malformed or sequestered parts of the alimentary canal, often forming gastrogenous or gastroenterogenous cysts. These are exemplified by the following unusual specimens.

Case 6

R 4584; by courtesy of Dr. H. S. Kellett, of Bradford.

In a mass radiographic examination a girl 18 years old was found to have a rounded anterior mediastinal mass, and this was removed surgically. It comprised a cyst 4 cm. in diameter enclosed in a mainly thin fibrous wall, in which, however, there were some thicker areas and some calcification. Microscopically, the main cyst is lined by ciliated pseudostratified respiratory epithelium, accompanied by some underlying glands, small cysts, and small cartilages. At one spot, however, this respiratory mucosa is replaced by intestinal mucosa, from which ducts extend out to connect with a small mass of pancreas (Fig 4, Special Plate). Some thymic tissue is incorporated in the outer layers of the cyst walls.

Comment.—The anterior situation of this cystic malformation, its respiratory epithelial lining, and the associated cartilages show that it is certainly bronchogenic in nature; its alimentary mucosa and pancreatic tissue must be attributed to heteroplastic differentiation.

In Case 6 the bronchogenic malformation was completely separated from the lungs. But some similar malformations lie within the lungs, and these also may show heteroplastic alimentary derivatives, as in two cases reported by Kellett, Lippard, and Willis (1962). In one of these mucosa and glands of gastrointestinal type had developed in the wall of an intrapulmonary cyst; and in the other, well-differentiated pancreatic tissue, with islands of Langerhans, was present, its lobules mingling closely with the bronchial cartilages and its ducts opening into bronchioles.

Case 7

R 4195; by courtesy of Miss B. V. Slessor, of Leicester, and Dr. G. R. Osborn, of Derby.

A baby girl who had had ptosis of the right upper eyelid and some breathlessness and snuffles from birth was admitted to hospital when she was 10 months old. Radiographs showed a large well-defined ovoid posterior mediastinal mass, and operation disclosed a huge cyst occupying most of the right side of the thoracic cavity from the neck to the diaphragm, displacing the lung forwards and to the left, and adherent to the oesophagus. It had no special vascular or other connexion with the lung, and it stripped readily away from neighbouring structures, except at its upper pole, where it adhered to the first rib and extended for a short distance up into the neck. The cystic mass removed comprised a large cyst and a number of smaller loculi, and measured 7 by 5 by 3 cm. Microscopically, the cavities are lined partly by respiratory, partly by stratified oesophagus-like, and partly by gastric mucosa, surrounded by thick smooth-muscular coats, external to which at one or two places there are plates of cartilage. There is no pancreas.

Comment.—Elsewhere (Willis, 1962a, p. 325) I have reviewed other reported cases of intrathoracic cysts lined wholly or partly by gastric mucosa, and have given the evidence that many of these arise from sequestered parts of the alimentary canal—that is, that they are gastroenterogenous in nature, not broncho-

genic. In Case 7 the presence of respiratory epithelium and of cartilage in some parts suggests that, despite its posterior position, this malformation may have been of bronchogenic rather than of gastroenterogenous origin. However, we cannot exclude a gastroenterogenous nature, for, as we will see presently, abdominal alimentary epithelium is capable of producing respiratory tissues by heteroplasia.

Case 8

R 3753; by courtesy of Dr. L. Wilkinson, formerly of Houston, Texas, now of Ridgewood, New Jersey.

A woman 48 years old had known for many years that she had an irregularity of her heart beat. When she was about 20 years old this had been diagnosed electrocardiographically as complete heart block. She had, however, remained well until a few days before her final admission to hospital, when she was found to have a moderate degree of hypertension, and after a few doses of a hypotensive drug she had an epileptiform convulsion and became unconscious. Examination in hospital, including electrocardiogram, confirmed the presence of heart block with a pulse rate of about 50 per minute. Soon after admission the patient had another convulsion and died. Necropsy revealed an area of abnormal fibrous and partly cystic tissue 2.5 by 2 by 0.3 cm. in the medial wall of the left atrium, just above the interventricular septum. Microscopically (Fig. 5, Special Plate), this area contains a variety of epithelial structures, some solid and partly squamoid, some forming gland-like vesicles or small cysts, in a number of which there is strongly eosinophilic secretion, while others show central granular calcification.

Comment.—This specimen exemplifies the very rare group of cases of congenital heart block due to epithelial inclusions in the course of the bundle of His, of which less than a score have been reported. These cases, some of which I have reviewed elsewhere (Willis, 1962a, pp. 330–332), all show a close resemblance to one another; the site of the anomaly is in the interatrial septum, and the epithelial inclusions are usually trabecular or tubular structures of rather non-distinctive characters. In the present case the resemblance of some of them to thyroid vesicles may be only fortuitous; or they may indeed be thyroid vesicles, since at least one instance of intracardiac thyroid tissue has been reported (Dosch, 1941). The mode of origin of epithelial inclusions in the heart is almost certainly by dislocation of a fragment of foregut endoderm into the dorsal mesocardium during the very early development of the heart rudiment, when this lies in close contiguity with the pharyngo-oesophageal rudiment, and especially with the thyroglossal outgrowth. I should add here that epithelial inclusions are a relatively rare cause of congenital heart block; a far greater number of cases of this are due to a primary failure of development of the bundle of His, with or without other cardiac malformations.

Endodermal Heterotopias in Abdomen

The commonest abdominal alimentary heterotopias are those seen in Meckel's diverticulum. In about 20% of cases this is lined by gastric mucosa, and every surgeon knows that this may suffer peptic ulceration with haemorrhage or perforation. In a smaller proportion of diverticula pancreatic tissue is present; and on occasion this too may cause surgical complications, as in the youth of 17 whose story I have recorded elsewhere (Willis, 1962a, Fig. 141), in whom acute haemorrhagic necrosis had supervened in the heterotopic pancreatic tissue.

Meckel's diverticulum is not the only part of the vitello-intestinal duct which may persist. Less frequently vestiges of this remain at the umbilicus, forming cysts, sinuses, or polypi; and these too often show gastric mucosa and sometimes pancreatic tissue. I have seen also one example of an ulcerated epithelial area on the surface of the umbilical cord which I

believe had resulted from peptic ulceration of a vitelline-duct cyst lined by gastric mucosa; and Dr. Mary C. L. Lee and Professor Kurt Aterman, of Halifax, Nova Scotia, have kindly shown me a pedunculated polypus of the cord 15 cm. from the umbilicus, clothed by small-intestinal mucosa and possessing a distinct muscularis mucosae and a rudimentary two-layered muscularis (to be published shortly in the *American Journal of Diseases of Children*). Presently I shall describe a specimen which raises the question whether the yolk sac in the placenta may produce heteroplastic derivatives.

Many malformations of the intestine, other than persistent vitello-intestinal vestiges, may show heterotopic tissues. This applies to diverticula at any site, to enterogenous cysts, and especially to duplications of the intestine, the supernumerary channels of which are frequently lined by gastric mucosa (Willis, 1962a, p. 190; Pugh, Feather, and Goldie, 1958). An example of gastric mucosa lining a closed cyst (R 4746) was given me by Dr. G. R. Osborn; this was a large kidney-shaped cyst which lay lateral to the caecum and which was surgically removed from a man 22 years old. Of special interest was a specimen shown me by Dr. J. C. Burne, of Dartford, and published by him in 1958. This was a diverticulum of the transverse colon from a girl 4 years old; its mucosa was partly gastric, partly duodenal, and partly like that of the appendix, and the wall contained a mass of pancreas. So far as I know this is the most distally situated of such heterotopias so far reported. The following is another very unusual—I believe unique—specimen of an intestinal diverticulum showing heterotopic tissues.

Case 9

R 4701; by courtesy of Dr. G. R. Osborn, of Derby.

A male infant 19 days old died of bronchopneumonia, and the malformation to be described was an incidental post-mortem finding. A diverticulum 2 cm. long and 1.5 cm. broad projected from the antimesenteric aspect of an upper coil of jejunum. Microscopically (Figs. 6–8, Special Plate), it is lined by a thick layer of stratified epithelium which is desquamating squames into the lumen; in its submucosa lie scattered compound racemose mucous glands, the prominent ducts of which are lined by a two-layered epithelium, which, however, becomes stratified as they traverse the well-developed muscularis mucosae to open into the lumen of the diverticulum. The diverticulum has a thick two-layered smooth-muscle coat, and an outer serosal coat with fatty tissue, nerves, some small lymph nodes, and one small lobule of pancreas. The most remarkable feature of all, however, is the presence of a prominent band of striated muscle fibres, measuring up to 5 mm. thick, which encircles the middle of the diverticulum outside its smooth muscular coat like an external sphincter (Figs. 6 and 8, Special Plate).

Comment.—In possessing this band of skeletal muscle as well as a smooth-muscle coat, and also in the nature of its lining epithelium and its associated glands and ducts, the diverticulum has a close histological resemblance to oesophagus. The only previous report that I know of oesophagus-like heteroplasia in the intestine is that of Aterman and Abaci (1967), who, in a male infant with some other malformations, found areas of oesophageal and gastric mucosa in the terminal ileum and caecum. The development of cross-striated muscle in the wall of the midgut is, so far as I know, a unique finding.

Before leaving the intestine I must refer to another extraordinary instance of heterotopia, which was reported by Marsden and Gilchrist (1963), of Manchester. Dr. Marsden kindly sent me sections and has allowed me to show photographs of the specimen. This was from a newborn baby girl who was operated on soon after birth because of exomphalos and ectopia vesicae. The sac of the hernia contained a dilated obstructed coil of terminal ileum, and 22 cm. of bowel was removed; the child was well eight years later. The dilated segment of ileum contained a rounded polypoid mass 3 cm. in

main diameter. Microscopically, the bulk of this consisted of well-differentiated lung tissue, including bronchial tubes with cartilages in their walls and bronchioles traversing lung parenchyma; but near the base of attachment of the mass to the bowel wall there were some squamous stratified epithelium, some gastric mucosa, and a small focus of pancreatic tissue. So far as I know, no other instance of heteroplastic differentiation of lung in the midgut has been reported, and Marsden and Gilchrist's case is unique.

Elsewhere (Willis, 1962a, p. 326) I have mentioned briefly a remarkable instance of heteroplasia in the urinary bladder; this was as follows.

Case 10

R 2910; by courtesy of Mr. D. S. Poole-Wilson and the late Dr. J. P. Smith, of Manchester.

A male infant 6 weeks old was admitted to hospital with a history of intermittent haematuria since birth. Intravenous pyelograms showed normal filling and functioning of both kidneys and ureters, and cystoscopy showed what appeared to be a tumour of the right anterior bladder wall. Total cystectomy, with transplantation of the ureters into the sigmoid colon, was carried out. The child did well until he was 3½ years old, when he rather rapidly became uraemic and died. The excised bladder contained, projecting into its cavity from its anterior wall, a cystic mass of irregular shape, 3 by 2 cm. This consisted of a thick muscular wall enclosing a large irregular cavity lined by rugose mucosa and communicating with the bladder cavity by a narrow orifice near the summit of the malformation, and a separate small cyst in one part of the wall of the main cavity. The vesical surface of the mass was clothed by smooth mucosa with slight superficial ulceration in places. Microscopically, this outer surface is partly transitional epithelium of vesical type, but partly gastric, with ulcerated areas. The cavity of the malformation is lined in different parts with gastric mucosa (Fig. 9, Special Plate), intestinal mucosa, and ciliated pseudostratified epithelium; and the separate small cyst also is lined by ciliated epithelium of respiratory type. The walls of the malformation contain plentiful smooth muscle and nerves, the muscle being arranged in distinct layers in parts.

Comment.—Here is a malformation of the bladder containing a variety of heterotopic alimentary tissues, and probably respiratory tissue as well. The possibility of its having been derived from an adjoining alimentary diverticulum which had adhered to and invaginated into the bladder was thought of but was excluded; at operation the bladder was unattached to the bowel, and the malformation was clearly intravesical. The possibility of its being teratomatous can also be excluded; it contains only alimentary and related tissues and none of the other common components of teratomas, and a true teratoma of the bladder has never yet to my knowledge been recorded. Can heteroplasia of the vesical tissues themselves be the explanation? In considering this question we at once recall that the bladder, as well as its allantoic diverticulum, the urachus, and also the urethra and prostate, are all derivatives of the endodermal cloaca, which is part of the embryonic hindgut, and therefore closely related developmentally to the large intestine. Since, as we have already seen, gastric and pancreatic tissue can be produced as far caudally as the transverse colon, why should not these or other heteroplastic tissues arise from still more caudal parts of the hindgut, including the bladder? The unique specimen that I have just described shows, I believe, that this can indeed happen.

Specimen of Heterotopic Liver in Placenta

My last specimen is not only a very unusual one but it is one which I discussed with Roy Cameron, who was particularly interested in it. It was as follows:

Case 11

R 4002; by courtesy of Dr. W. D. Nicoll, Ayrshire.

A woman aged 26 with obvious hydramnios was admitted to hospital in labour in the 28th week of pregnancy. The very small premature infant, who had complete bilateral harelip and cleft palate, died soon after birth. The placenta was retained; and on its attempted removal another mass of tissue had to be removed first. Most of this was free, but it was attached to the placenta at one part. The placenta proper was removed piecemeal and was not submitted for examination. The paraplacental mass measured 10 by 12 by 6 cm. and had a slightly lobulated smooth surface, except for irregularities and a deep cleft on one side; on section it had a variegated appearance, being partly spongy and partly solid in texture and showing areas of necrosis. Microscopically, many sections from all parts of it show that most of it has the structure of a partly canalized and partly non-canalized haemangioma (Fig. 10, Special Plate), but that it contains also, near the deep cleft on its irregular placental surface, a mass of well-differentiated foetal liver about 3 cm. in main diameter. Some of this is in the form of compact well-circumscribed lobules (Fig. 11, Special Plate), but in other places it mingles with the haemangiomatous tissue, and indeed much of it shows clumps and trabeculae of liver cells separated by excessive vascular channels—just as in the rare condition of congenital haemangiomatosis of the liver. No definite bile ducts can be distinguished. Active haemopoiesis is evident in most parts of the hepatic tissue (Figs. 11 and 12, Special Plate). Careful search of many sections fails to discover any other tissues than those described.

Comment.—Here, then, we have a large haemangioma, resembling those that are well known in or attached to the placenta, but remarkable—so far as I know, unique—in containing also a mass of liver tissue. How did this arise? There are four distinct hypothetical possibilities to consider. (1) The first possibility is that part of the infant's own liver suffered evagination and became attached to the placenta; this possibility can be excluded, because necropsy was performed on the infant and showed that its liver and other viscera and its abdominal wall were normal. (2) The second theoretical possibility is that the accessory liver tissue is that of an acardiac twin, all the other tissues of which have disappeared. This hypothesis also can, I think, be discarded, since the very tissues which reduced acardiacs are most deficient in are their thoracic and abdominal viscera, especially the liver; it is inconceivable that an acardia could be reduced to liver only. (3) A third possibility, that the angiomatous and hepatic tissues are components of a placental teratoma, is in the highest degree unlikely, for placental teratomas of any kind are great rarities, liver tissue is a rare component in teratomas of any site, and in the present case thorough search has failed to find skin, nervous tissues, or any of the other common components of teratomas. (4) We are left, then, with our fourth possibility—namely, that the liver tissue in this case is a heteroplastic derivative of the vitello-intestinal vestiges, either the yolk sac in the placenta or possibly a persistent remnant of the duct in the cord. Both Roy Cameron and I came to the conclusion that this was much the most likely explanation, and I would like to outline to you our reasons for this.

Besides the extreme improbability of the other three ideas that I have mentioned, we recalled the fact that the vitello-intestinal epithelium in all of its well-known situations in the embryo and foetus displays a great capability for heteroplastic differentiation and growth. Since this epithelium in Meckel's diverticulum and at the umbilicus often develops into gastric mucosa and often produces outgrowths which differentiate into pancreas, why should not the same epithelium in the yolk sac have similar potentialities? May it be that heteroplastic derivatives of the yolk sac do sometimes occur in the placenta, but that they are not discovered because they are hidden away and because the placenta is not often examined very thoroughly? Assuming that the liver tissue in Case 11 did indeed arise from the yolk-sac endoderm, we may legitimately speculate a little further about why liver rather than gastric or pancreatic tissue should have developed here.

There are reasons for suggesting that this may have been related to the peculiar vascular environment provided by the placenta. Just as the normal liver develops by proliferation of an outgrowth of the gut, forming cords and sheets of hepatic cells which penetrate intimately between the sinusoidal channels of a richly vascular plexus derived from the vitelline veins, so it may be that, if the yolk-sac endoderm were to proliferate, and especially if it were to retain its primitive vitelline circulation along with the allantoic one, it might, in response to the vascular bed in which it was growing, undergo differentiation into liver tissue.

In this connexion it is pertinent to recall a specimen that was described and depicted before the end of last century by Ballantyne (1902, p. 155)—a full-term placenta with an unusually prominent yolk sac and a prominently persistent vitelline circulation. A significant feature of our specimen of placental liver tissue is its close association with a large haemangioma. This association surely cannot be fortuitous; it gives further evidence that vascular conditions in the placenta may well have been the factor which determined the heteroplastic development of liver from a proliferating yolk sac. Finally, I would urge that in examining any specimens of placental haemangioma—a rare but well-known anomaly—special search for persistent vitelline vessels, for the yolk sac, and for possible heteroplastic derivatives of it should be made.

Conclusion

In this talk I have glanced at the structural evidence, provided by a number of unusual malformations, which shows that the endoderm of the embryonic gut is highly plastic from end to end, and capable at almost any level of the body of aberrant differentiation to form tissues appropriate to other and distant levels. We have seen that heteroplastic gastric and pancreatic tissues, both often present in malformations of the abdominal parts of the alimentary canal, are not confined to these parts but can develop also at higher levels—in the thorax, from either the alimentary canal itself or the respiratory outgrowth, and even from the extreme anterior part of the gut in the mouth region. Conversely, abdominal parts of the gut can produce differentiated structures appropriate to higher levels, as in the jejunal diverticulum with oesophagus-like structure, even to the acquisition of cross-striated muscle (Case 9), and Marsden and Gilchrist's specimen of lung in the lower ileum. Furthermore, the heteroplastic formation of alimentary and respiratory tissues is not confined to the alimentary and respiratory systems; it can occur also in the bladder, an organ which, though separated from the alimentary canal at an early stage of development, is a derivative of the extreme caudal end of the primitive gut. And lastly we have seen two specimens which show that even liver tissue can arise at widely different levels of the gut—in one case from its anterior extremity in the mouth region, and in the other from its extra-embryonic vitello-intestinal vestiges in or near the placenta.

Finally, I must mention briefly a subject which particularly interested Roy Cameron—the manifestations of function in the heterotopic tissues. That heterotopic gastric mucosa secretes acid and enzymes is shown by its peptic ulceration, a well-known complication in Meckel's diverticulum, and one which has also been seen in intrathoracic cysts, in some cases with perforation of the ulcer into the pleural cavity or into a bronchus. That heterotopic pancreas is functional is suggested by its perfect structural differentiation, often including plentiful islets of Langerhans; and it is perhaps significant that it may suffer from acute haemorrhagic necrosis, as in one of my specimens. But I do not know of any enzyme or glucose-tolerance studies in patients with heterotopic pancreas, the presence of which, of course, is not suspected until the malformation bearing it has been removed. In the two cases of heterotopic liver which I have described, again we have only their

structural perfection to suggest that they were functional; and it is noteworthy that in both cases active haemopoiesis was in progress in the hepatic tissue.

I conclude with the following words of Sir James Paget (1882), who, writing about the structural study of malformations, said: "Not one of them is without meaning; not one that might not become the beginning of excellent knowledge, if only we could answer the question—why is this rare? or, being rare, why did it in this instance happen?" Roy Cameron set a perfect example of that nicely balanced combination of morphological and experimental inquiry which is essential for elucidating *why things happen*.

I am deeply indebted to many fellow pathologists for sending me the specimens described and for their permission to record them; I have given their names in the case reports. Most of the photographs are the work of Mr. Gerald Leach, of the Imperial Cancer

Research Fund, London; and to him and to Dr. Stretton Young, head of its Division of Pathology, I am very grateful.

REFERENCES

- Aterman, K., and Abaci, F. (1967). *Amer. J. Dis. Child.*, **113**, 552.
 Ballantyne, J. W. (1902). *Manual of Antenatal Pathology and Hygiene*, vol. 1. Edinburgh.
 Burne, J. C. (1958). *J. Path. Bact.*, **75**, 470.
 Dosch, F. (1941). *Beitr. path. Anat.*, **105**, 244.
 Kellett, H. S., Lippard, D., and Willis, R. A. (1962). *J. Path. Bact.*, **84**, 421.
 Lee, M. C. L., and Aterman, K. (1968). *Amer. J. Dis. Child.* In press.
 Marsden, H. B., and Gilchrist, W. (1963). *J. Path. Bact.*, **86**, 532.
 Paget, J. (1882). *Lancet*, **2**, 1017.
 Pugh, R. J., Feather, D. B., and Goldie, W. (1958). *Brit. J. Surg.*, **46**, 83.
 Schultz, L. (1927). *Arch. Path. Lab. Med.*, **4**, 359.
 Willis, R. A. (1962a). *The Borderland of Embryology and Pathology*, 2nd ed. London.
 Willis, R. A. (1962b). *Pathology of the Tumours of Children*. Edinburgh and London.

Detection of Allergy to Penicillin and Other Antigens by In-vitro Passive Sensitization and Histamine Release from Human and Monkey Lung

E. S. K. ASSEM,* PH.D., M.R.C.P.; H. O. SCHILD,† M.D., PH.D., D.SC., F.R.S.

Brit. med. J., 1968, **3**, 272–276

Summary: Preparations of chopped human and monkey lung were used to estimate the reagin activity of serum from allergic patients. The lung preparation was passively sensitized by incubation with serum taken from the patients, and then challenged with the antigen responsible for the allergy. Measurement of the histamine released from the lung gave a quantitative assessment of the level of reagin activity in the patient's serum.

Tests were done on patients allergic to four natural antigens, including grass pollen, and to penicillin. Human lung proved more sensitive and possibly more specific than monkey lung in testing for natural allergies. The results of testing for penicillin allergies were less satisfactory, possibly because of the difficulty of reconstructing the appropriate antigen.

Introduction

Histamine release from the tissues of an allergic individual was first demonstrated by Katz and Cohen (1941), who found that whole blood of a subject with ragweed hypersensitivity liberated histamine when incubated with antigen. It was later shown that pieces of lung removed at operation from a pollen-allergic patient released histamine when incubated with pollen (Schild, Hawkins, Mongar, and Herxheimer, 1951). Histamine liberation from whole blood or isolated human leucocytes by incubation with a specific antigen has since been made into a quantitative procedure (Noah and Brand, 1955; VanArsdel, Middleton, Sherman, and Buchwald, 1958; Lichtenstein and Osler, 1964).

The tests discussed so far reflect active sensitization and are essentially comparable to the weal and flare reaction which follows the intradermal injection of an antigen in a sensitized patient.

Another set of tests, also based on histamine release, is concerned with the demonstration of circulating reagins. These involve the passive sensitization of normal tissues with allergic sera in vitro followed by antigen addition and histamine release. These tests are essentially comparable to the Prausnitz-Küstner reaction, in which the serum of an allergic patient is injected intradermally into a normal subject, who is then tested with the antigen. Procedures of passive sensitization of normal tissues in vitro followed by histamine release with antigen were first developed for chopped guinea-pig lung (Mongar and Schild, 1957b; Brocklehurst, Humphrey, and Perry, 1961), but guinea-pig tissue is unsuitable for the measurement of human reagins, which will sensitize only human or other primate tissues (Benacerraf, 1968). Human tissues which are suitable for passive sensitization and histamine release in vitro are normal leucocytes (Middleton, Sherman, Fleming, and VanArsdel, 1960; Lichtenstein and Osler, 1964) and chopped lung (Parish, 1967; Sheard, Killingback, and Blair, 1967; Augustin, 1967; Bukhari, 1967; Brocklehurst, 1968); a suitable monkey tissue is chopped lung (Goodfriend, Kovacs, and Rose, 1966).

In the present study human and monkey chopped lung has been used, and the suitability of the two species for the detection and measurement of the reagin activity of human serum compared. The initial experiments were carried out with sera of patients allergic to pollen and other environmental antigens. The establishment of a drug reactions reporting system at University College Hospital has proved an opportunity of studying a number of patients with penicillin allergy and to investigate whether they carried reagins capable of sensitizing lung tissue in vitro.

Material

Penicillin Allergy.—Twenty-two patients were investigated for penicillin allergy; in eight of these (Cases 12–19) the clinical diagnosis of penicillin allergy was established, as these patients "reacted" to penicillin on two or more occasions.

* Wellcome Research Fellow, Department of Pharmacology, University College, London, and Medical Unit, University College Hospital Medical School, London W.C.1.

† Professor of Pharmacology, University College, London W.C.1.