Paediatric Pathology

Edited by

Colin L. Berry

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With Contributions by
Robert H. Anderson, Anton E. Becker, Mies J. Becker,
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Peter A. Revell, R. Anthony Risdon, Joseph F. Smith, Michael Swash

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Preface

The increased provision of facilities for neonatal and paediatric care in the last 25 years has been accompanied only in part by appropriate developments in pathology. Specialist pathologists are many fewer than paediatric departments, and details of the advances in knowledge of the pathogenesis of diseases in childhood and of ways of investigating them are not uniformly available. In many institutions an individual with a special interest rather than a special training will be responsible for paediatric pathology and it is to this group of histopathologists that this text is addressed. For this reason it is not written as a comprehensive text and is not intended for use as a reference volume. Areas which may produce particular difficulties for the individual with little specialist knowledge of the very young (e.g., the lung) are dealt with in more detail and, in general, entities in which the histopathology does not differ greatly from that of the adult disease are considered briefly. A brief account of developmental processes is included where prenatal considerations are helpful in understanding a particular entity. A number of specialist topics which are known to trouble those who work in nonspecialist departments are described fully (diseases of muscle) or with guides to investigation (metabolic disease). The value of investigation and careful description of abnormalities of development is also emphasized.

The authors are from different backgrounds, paediatric pathologists (J. W. Keeling, J. Cox), pathologists in general departments with extensive experience in paediatric pathology (C. L. Berry, R. A. Risdon, M. Becker, J. Smith) or specialists with an interest in the manifestation of diseases of which they have expert knowledge in the young (P. A. Revell, R. H. Anderson, C. L. Brown, M. Swash, A. E. Becker, B. D. Lake). All are valued and respected friends, who have been asked to contribute in a particular way; any errors of 'design' are my own.

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Contents

Chapter 1

Examination of the Fetus

Colin L. Berry

In many pathology departments products of conception are not examined in detail and sections are taken only to confirm pregnancy. Much information can be obtained from these specimens, which may be of value in genetic counselling or in the management of future pregnancies. The occurrence of congenital heart disease, facial clefts, or neurospinal defects in embryos and early fetuses all have considerable predictive value in terms of the likely outcome of future pregnancies, and may help to ensure that screening techniques (e.g., α-fetoprotein determinations) are used in individuals at risk. Although many relatively complex procedures may be used on material from abortions, including cell culture with subsequent enzymatic or metabolic studies, these are not practicable in most instances or in any but a few laboratories. Nor is it desirable that they should be carried out in many centres; as Benson et al. (1979) have pointed out, there are considerable advantages in terms of experience and the control of assay techniques in carrying out tests for metabolic disease in only a few centres. It has also been estimated that less than 120 pregnancies will be known to be at risk of metabolic disease in the United Kingdom in a year, suggesting that a few centres could cope with the likely workload.

This figure contrasts sharply with the 15 000 or so infants delivered with major congenital defects each year. If the increased incidence of defects found in early pregnancies is considered (p. 68) it is evident that most histopathological laboratories receive abnormal fetuses every year, although few are documented in detail. An example of a defect that can be diagnosed by inspection in early pregnancy is shown in Fig. 1.1.

Simple morbid anatomy and histopathology will provide useful data on embryonic and fetal material, and require only a dissecting microscope and X-ray facilities. Specimens are often received incomplete, fragmented, with or without the placenta, and usually fixed. The techniques recommended take note of these constraints. Detailed accounts of abnormalities are not given here, but can be found in the relevant chapters. Further technical details can be found in Berry (1980).

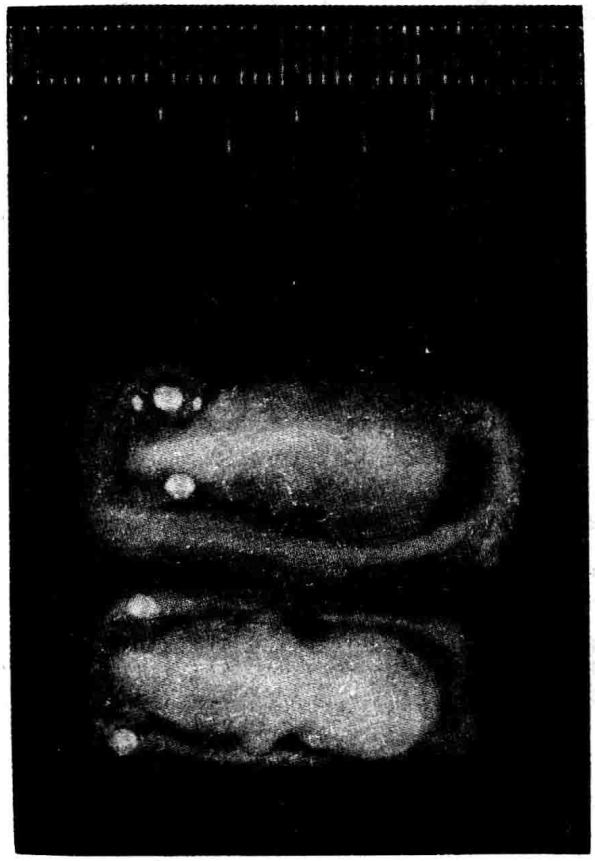

Fig. 1.1. Webbed 'neck' in an early (34-mm) embryo with Turner's syndrome. (45 ×) A control embryo is also shown.

1. History

As with all surgical specimens, a good history is important but not always provided. The date of the last menstrual period is an essential piece of information if findings are to be properly interpreted. Knowledge of previous reproductive performance is valuable, and the mode of induction of abortion should be stated, if it is not spontaneous.

2. Dimensions

Many measurements can be made on fetal and embryonic specimens, but there are considerable difficulties with a number of them. Crown–heel lengths measured by different observers under normal laboratory conditions vary considerably, as do crown–rump (CR) measurements. Table 1.1 provides average values for the latter variable, based on a number of series. There is wide variation, however, which depends largely on the reproducibility of the position of the fetus and its degree of maceration. Careful studies such of those of Bagnall et al. (1975) and Birkbeck et al. (1975a) show the value of CR and crown–heel measurements, but for a pathological laboratory the measurement of foot length is simpler and provides comparable data. Foot length is not affected significantly by fixation or maceration, and an intact foot is often found where the fetus is received in fragments. Data relating foot length to CR length and gestational age, based on the work of Streeter (1920) and Trolle (1948), are shown in Fig. 1.2; figures for later pregnancy from Usher and McLean (1969) are shown in Table 1.2. Foot length has the additional advantage that it is seldom directly affected by malformation—for example anencephalic fetuses have normal foot lengths (Nañagus 1925) though they are otherwise difficult to measure.

Table 1.1. Change in crown-rump length (CR) with age

Day	CR (mm)	Day	CR (mm)
35	8	127	134.5
42	15	134	146.0
49	22	141	156.5
56	29.5	148	167.0
63	40.0	155	177.5
70	50.5	162	188.0
77	61.0	169	198.5
84	71.5	176	209.0
91	81.5	183	219.5
98	92.0	190	230.0
105	103.0	197	240.5
113	113.5	204	251.0
120	124.0		

Table 1.2. Later gestational age–foot length correlations (Usher and McLean 1969)

Gestational age (weeks)	Foot length (mm)[a]
27–28	55.4 (3.08)
29–30	57.7 (2.12)
31–32	62.6 (3.32)
33	67.4 (4.78)
34	69.6 (3.76)
35	71.4 (3.76)
36	72.8 (4.12)
37	78.0 (3.91)
38	78.2 (4.11)
39	77.3 (3.56)
40	78.4 (3.45)

[a]Figures in parentheses give SD.

3. Weights

The weights of the placenta and fetus should be determined. Determination of fetal age by weight alone is always imprecise (see Birkbeck et al. (1975b)), but marked disproportion between placental and fetal weight may be informative.

There is no doubt but that accurate measurement of placental weight is very difficult; different authors have trimmed different parts of the membranes, cut off the cord, drained blood from the organ before weighing, etc. The most accurate measurement of the weight of placental tissue is obtained after homogenization of the organ and estimation of the haemoglobin in the homogenate; if the value of haemoglobin in cord blood is assumed to be the same as that in the placenta a correction for the weight of the contained blood can be made.

This is clearly impracticable as a routine technique. In general the determination of placental weight in early pregnancy is unhelpful. Fetal weight is exceeded by placental weight until week 14–15 (100 mm CR length, 17 mm foot length), when the placental growth rate falls and that of the fetus increases rapidly. The data of Boyd and Hamilton (1970) are often cited for relative weight, and tables have been constructed from arithmetic regression based on their data. The scatter in the original observations is enormous and, in the author's view, permits only limited statements. At 200 g fetal weight the placenta usually weighs 120 ± 20 g, and at a fetal weight of 1000 g the placenta weighs 250 ± 50 g. For figures for later pregnancy (32 weeks

onward) the data of Thomson et al. (1969) for gross placental weight, in which the placenta has not been manipulated or trimmed in any way, are preferred. Fetal and placental weights in early pregnancy are shown in Table 1.3.

Table 1.3. Fetal and placental weight (date from Boyd and Hamilton 1970)

Weeks	CR length (mm)	Fetal wt. (g)	Placental wt. (g)
4–8	5– 30	0.5– 2.9	5.0– 27.0
8–12	31– 60	2.7– 25.0	10.0– 80.0
12–16	61–100	11.0–135.0	28.0–134.0
16–20	101–155	57.0–350.0	55.0–198.0

4. Dating

External examination, careful measurement, infinite technical resources (serial sectioning), and precise historical details will allow most embryos and fetuses to be dated with accuracy. This is neither possible nor necessary in routine practice, and the 'markers' given here are those that any laboratory can determine readily. Dating should be carried out on the basis of several sources of data (history, external form, size, weight, morbid anatomy, and histological development).

5. Chronology of Early Pregnancy in Man

If day 1 is considered to be the day on which a fertilized egg is present in the Fallopian tube, on day 2 there will be a 2- or 4-celled mass present. On day 3, an 8- to 12-celled mass is found, on day 4 the blastocoele begins to develop, and on day 5 a free blastocyst is found in the uterus. The blastocyst begins to implant on day 6 and implantation is not complete until day 13–14.

Morphological developmental indicators found by certain times are shown in Tables 1.4 and 1.5. These are readily identifiable in selected blocks and demonstration of them does not require serial sectioning. Between 12 and 20 weeks axial skeletal development provides a useful guide (see Fig. 1.3).

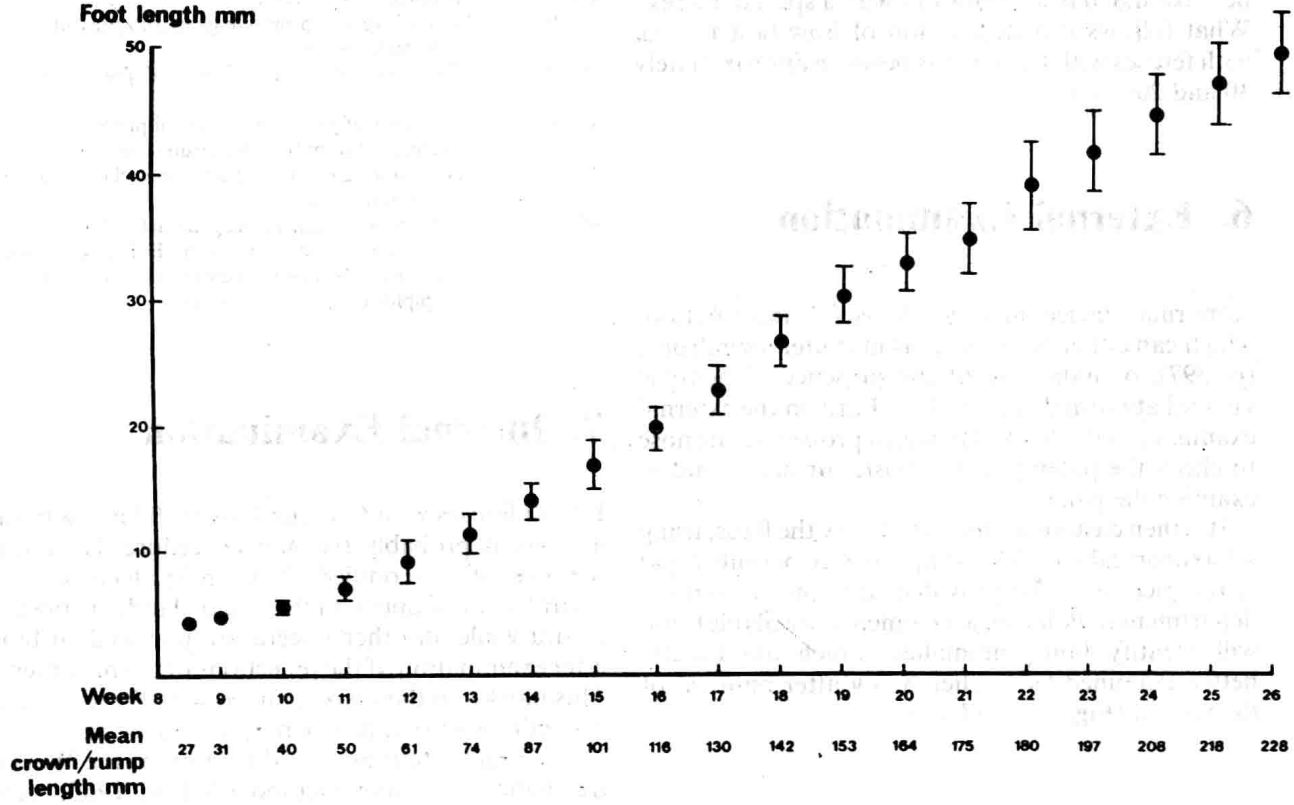

Fig. 1.2. Correlation of foot length with crown–rump length of human fetuses.

Table 1.4. Morphological markers of development

Time (days)	System					
	Central nervous	Cardiovascular	Urogenital	Gastrointestinal	Respiratory	Other markers
28	Anterior neuropore closed Cerebral vesicles present Lens placode reaches optic cup	Septum primum present	Metanephros forming	Oesophagus separated from trachea Liver bud present Dorsal pancreatic component present	Lung primordium established Trachea and primitive bronchi present	Thyroid in mid-line
35	Lens pocket closes	Ventricular septum and semilunar valves forming	Ureteric buds develop Germ cells in genital ridges			Spleen in dorsal mesogastrium
42	Semicircular canals Neurohypophysis develops	Truncus divides, septum secundum appears	Major calyces appear	Hepatic haematopoiesis begins Hernia of umbilical loop	Capillaries in lung parenchyma	Thymus and parathyroids arise from branchial pouches Paddle-shaped hand
50	Lens vesicle a 'full' sphere Eyelids developing	Ventricular septum complete	Paramesonephric duct Seminiferous tubules as solid strands	Palatal shelves and salivary glands develop		Thymus invaded by lymphocytes Separate digits

Embryos can seldom be examined in sufficient detail in routine laboratories, although our knowledge of the morphology of early human malformations is scanty and such studies would be valuable. Serial sectioning is clearly impracticable, and if abnormal embryos are found they are often best examined in a laboratory with a special interest. What follows is a description of how best to deal with fetuses with CR lengths between approximately 30 and 200 mm.

Table 1.5. Later morphological markers

Age in weeks	Finding
10	Fingerprints present
11	Gut loops return to abdomen
20	Bronchi cease budding
22–25	Three layers of primitive glomeruli present. Alveoli appear
25–28	Two layers of primitive glomeruli present. Eyelids open
28–30	One layer of primitive glomeruli present
31	Occasional primitive glomeruli seen
36	No further glomerulogenesis. Ears flat. Breast $\simeq$3 mm diameter
40	Ears show cartilage ridges. Breast $\simeq$7 mm diameter. Testes in scrotum. Full foot creases present. Ossification centres in lower femoral epiphysis, calcaneus and talus

6. External Examination

Abnormal facies may yield useful information, which can either be specific, as in Potter's syndrome (p. 397), or indicative of the presence of possible visceral abnormality (Fig. 1.4). Early in the external examination it is helpful to pass a probe into the nose to check the patency of the posterior nares, and to examine the palate.

It is then customary for us to X-ray the fetus, using a Faxitron cabinet. This simple device permits rapid X-ray pictures to be provided promptly within the department (a Polaroid attachment is available), and will identify bony anomalies, which are usually better examined by further X-ray after removal of the viscera (Figs. 1.5 and 1.6).

7. Internal Examination

For all fetuses with CR length over 100 mm a mini-autopsy is probably the best procedure. However, the use of a modified Rokitansky technique is desirable, the kidneys, ureters, and bladder being left in situ while all other viscera are removed en bloc after examination of the reflections of the mesentery. This block can then be examined with the aid of the dissecting microscope when necessary.

For smaller fetuses a modification of the Wilson free-hand sectioning method (Wilson 1965) used extensively on rodents in teratological studies should

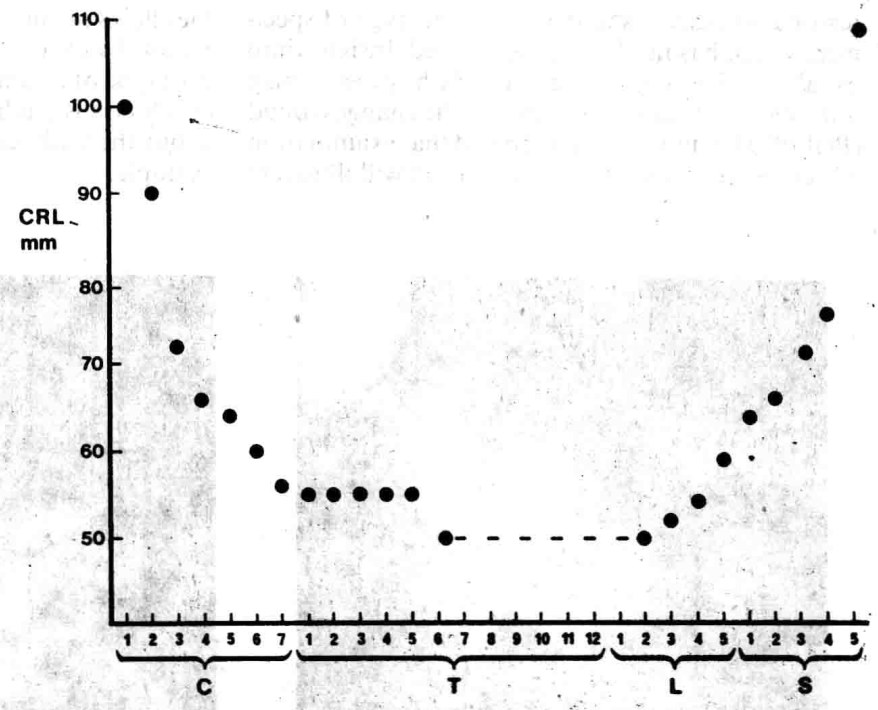

Fig. 1.3. Scheme of appearance of vertebral body ossification centres. These are first evident in the lower thoracic region, and spread up and down the spinal column as shown.

be employed. This involves cutting the trunk of the embryo into slices approximately 2–3 mm thick, which are examined from above and below by dissecting microscopy. This technique is simple and thorough (Figs. 1.7 and 1.8).

Following removal of the viscera the skeleton is again X-rayed. This gives a good picture of the axial skeleton, which apart from specific abnormalities provides useful information on dating.

Where any tissue appears abnormal, or any organ seems to be too large or too small, a block should be taken.

8. Abnormalities of Specific Systems

When macroscopic anomalies are found the standard technique is often abandoned.

8.1. Central Nervous System

In general, anomalous portions of the central nervous system should not be dissected as wet specimens. The cerebrospinal axis may be preserved as a unit, and cut in large sections or transversely in a number of blocks (see Fig. 1.9). Recent reports (Granchrow and Ornoy 1979) have emphasized the value of

Fig. 1.4. Fetus affected by Meckel's syndrome. Encephalocoele is present and horseshoe kidneys, shown to be dysplastic, are also seen. The liver showed cystic bile ducts in histological sections.

histopathological examination of this type of specimen, which has rarely been performed. Insights into or alternative suggestions for pathogenesis may follow accurate documentation of the changes found (Bell 1979). It must be remembered that examination of neurospinal malformations at term will illustrate the effects of injury or abnormality followed by up to 8 months of attempted repair and further growth. This type of examination, where only the 'late' stage of a lesion is studied, would yield little information about the pathogenesis of a contracted kidney, for example.

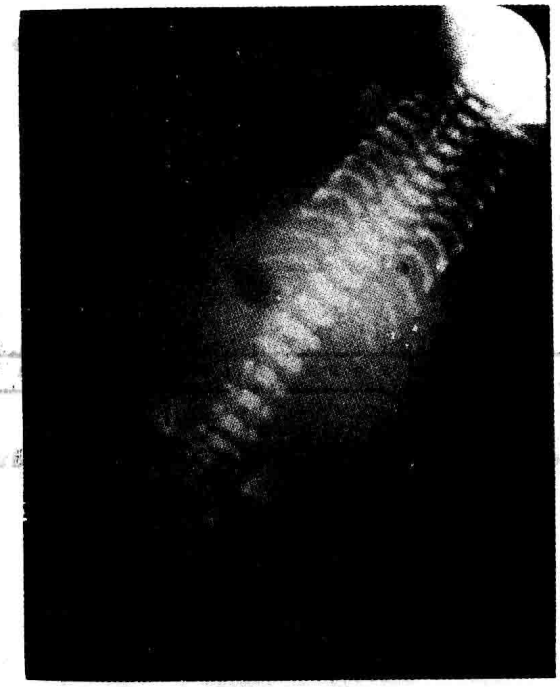

Fig. 1.5. Abnormal rib development in asphyxiating thoracic dystrophy. (Courtesy of Dr. A. B. Bain).

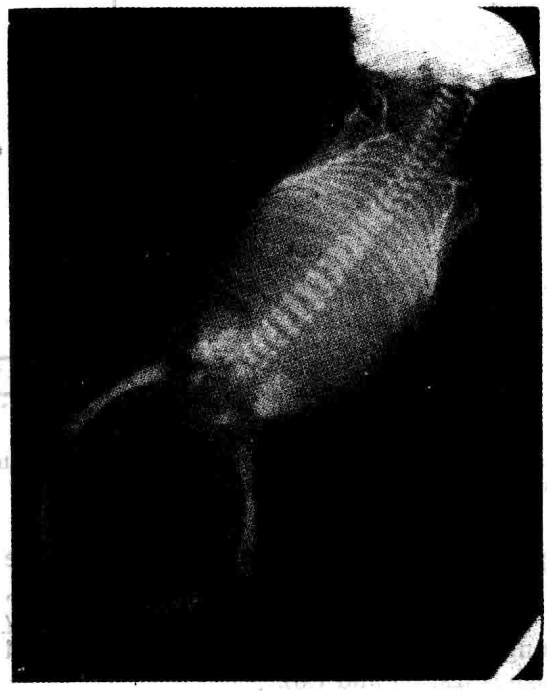

Fig. 1.6. Bell-shaped thorax in pulmonary hypoplasia, a change seen in several conditions, including Potter's syndrome.

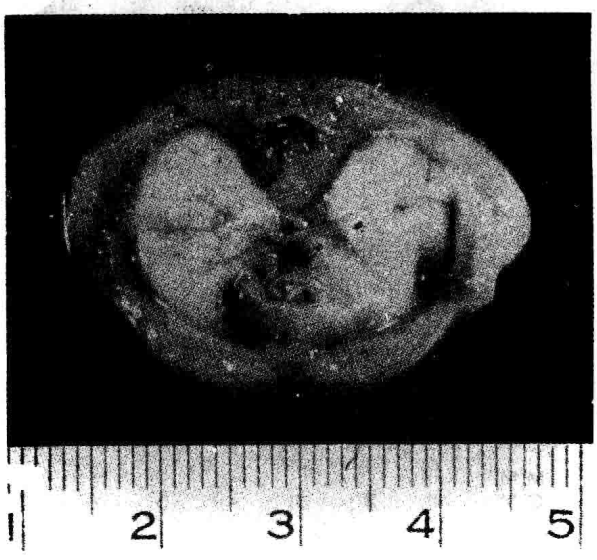

Fig. 1.7. Slice of fetus at the level of the great vessels.

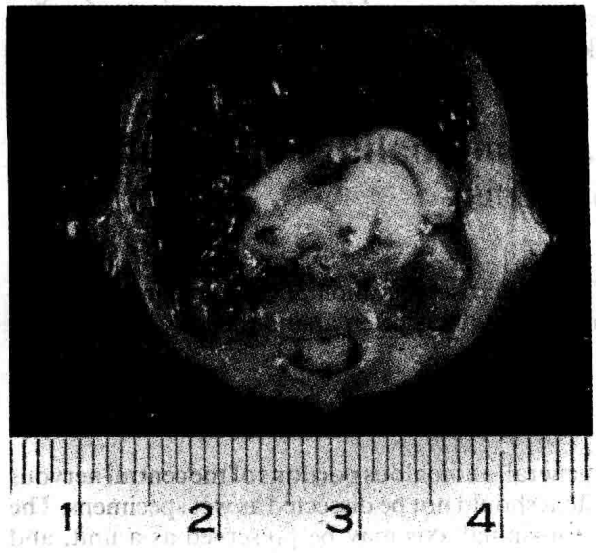

Fig. 1.8. Upper abdominal slice showing kidneys and liver, viewed from below.

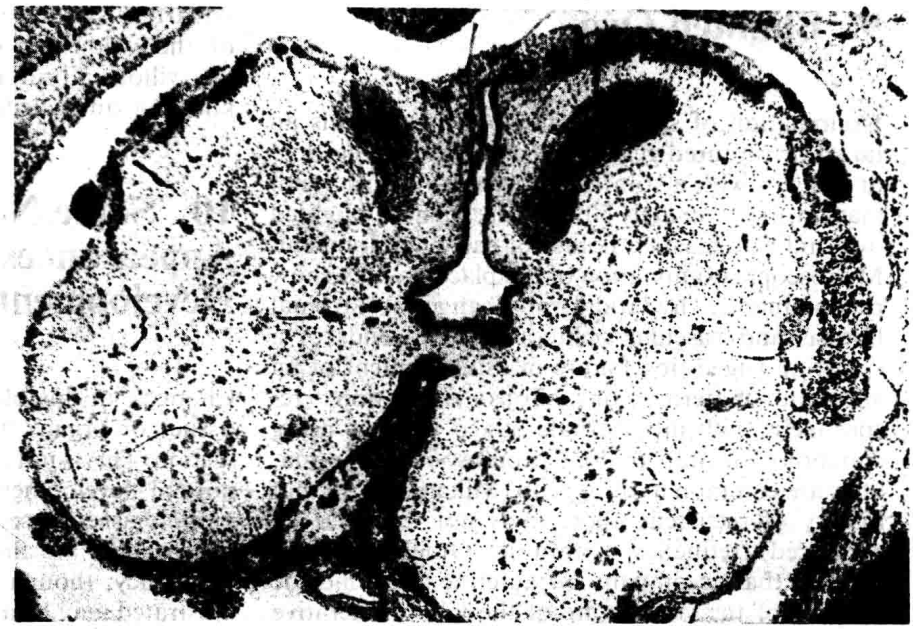

Fig. 1.9. Section of spinal cord above lumbo-sacral meningomyelocoele. The abnormal central canal and partial division of the cord extend dorsally for several vertebral bodies above the defect. From a fetus terminated at 20 weeks for dysraphism. (Methacrylate section; trichrome stain; ×40)

8.2. Cardiovascular System

Even without an extensive knowledge of the vastly complex field of congenital heart disease a useful assessment of anomalies can be made if the system of Tynan and his colleagues is used (see Tynan et al. 1979 and Chap. 4, where the method is described in detail). If the heart is classified in this way a description may be of considerable value to those expert in the field or for later checking, in an area where photography is difficult and where the heart may not always be kept.

8.3. Musculoskeletal System

Musculoskeletal abnormalities are well illustrated by X-ray, but valuable data can be obtained by section. For example, extra digits can be defined by checking muscle insertions to see whether a 'thumb' is really a finger. Abnormalities of the digits have not often been described so carefully, but the information obtained from this type of examination would permit more critical analysis of limb defects. Animal studies suggest that this would be valuable in man. [See, for example, the work of Theisen et al. (1979) with thalidomide.]

8.4. Urogenital System

After removal of the other viscera, the kidneys and ureters should be freed from the posterior abdominal wall. The pubes are then split and the pelvic viscera removed. Dissection, or fine probing, will then reveal where aberrant ureters drain, or whether fistulae exist. Fine polythene catheters, heat-sealed at their ends, make good probes.

8.5. Metabolic Abnormalities

Prenatal diagnoses are usually made in selected groups. These include women over 35 years of age being screened for chromosomal abnormalities and women who have previously given birth to an infant affected by a malformation, e.g., neurospinal dysraphism. Metabolic disorders are usually sought only after an affected child has been diagnosed, which emphasizes the value of examining abortion material. It is clearly absurd to suggest, however, that all abortuses are examined for possible metabolic disease, so the role of the pathologist is to look out for abnormalities that might be associated with metabolic disease. Foam cells in the placenta or central nervous system suggest lipidosis, while some of the skeletal anomalies of the mucopolysaccaridoses are recognizable in fetal material, as are some features of the glycogenoses. Seventeen types of lipidosis, 11 of mucopolysaccharidosis, 22 of amino-aciduria or related disorders, 11 defects of carbohydrate metabolism, and 26 miscellaneous disorders have been diagnosed antenatally; a further 7, 7, 17, 8, and 15 disorders are potentially diagnosable in each category, respectively (see Milunsky 1976).

Alerting a clinical colleague to the possibility of the presence of such a disorder is of major importance in preventive terms.