Visceral Variations and Defects Associated with Cleft Lip and Palate in Human Fetuses: A Macroscopic Description

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It is well known that the condition of cleft lip and palate in the human frequently occurs in association with other external malformations. In a previous paper (*3*) the kind and frequency of gross external malformations associated with cleft lip and palate in human fetuses was reported. Little is known about the kind and frequency of visceral anomalies and defects in such cases.

The literature on this subject mainly concerns associated anomalies of the heart. Sinclair and MacKay (*7*) reported on a cleft palate infant with a very small heart. Caramelli and Reginato (*1*) described a variety of heart anomalies which were found in association with cleft palate in infants. Potter (*5*) dealt with a case of hypoplastic adrenals in an infant with cleft lip and palate. Reports on laboratory animals have been made by Wilson and Warkany, cited by Warkany (*9*), in the case of rats associated cardiac and urogenital anomalies, and by Fitch (*2*) in the case of mice with associated anomalies of the heart, thymus, intestines, and ovary.

Material and Method

Ninety human fetuses were studied in this investigation. They were selected from a large collection of aborted human fetuses obtained from hospitals throughout the United States as well as in Japan. Thirty of these specimens were affected with clefts, ranging from clefts of the lip to complete clefts of the primary and secondary palate. The remaining 60 noncleft fetuses were selected on the basis of their freedom from obvious external malformations (including clefts). The fetuses ranged in age from seven to 19 weeks as estimated from crown-rump lengths (*4*). The sample was selected so that for each cleft specimen there was at least one noncleft fetus comparable in age and sex. This facilitated comparison of the visceral organs in cleft and noncleft fetuses. The morphology of all the

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thoracic and abdominal organs was observed in detail with the aid of a dissecting microscope.

Results

NATURE AND FREQUENCY OF AFFECTED ORGANS. Most of the fetuses used in this study, whether affected by cleft palate or not, were observed to have considerable variation in visceral form. These data are presented in Tables 1, 2, 5, and 7. In 30 cleft fetuses there was a total of 306 visceral anomalies, whereas in the 60 noncleft specimens there were 210 anomalies. This high incidence is in part due to the occurrence of several different interrelated anomalies in the same organ. It was noted that there was a high frequency of anomalies in the noncleft group for lung, spleen, heart, and liver. In the cleft group, there was a high frequency of anomalies of the lung, heart, spleen, stomach, liver, kidney, intestine, gonads, thyroid, thymus, and adrenals.

TABLE 1. Mean number of fetuses with visceral anomalies and mean number of affected visceral organs for cleft and noncleft groups.

Group	*N*	*Visceral Anomalies*		*Affected Organs*	
		N	*M*	*N*	*M*
Cleft	30	306	10.2	191	6.3
Noncleft	60	210	3.5	182	3.0
Total	90	516		373	

TABLE 2. Numbers and percentages of the 30 cleft and the 60 noncleft fetuses which had affected visceral organs.

Affected Organ	*Cleft Fetuses*		*Noncleft Fetuses*	
	N	*%age*	*N*	*%age*
Lung	25	83.3	47	78.3
Heart	22	73.3	20	33.3
Stomach	10	33.3	3	5.0
Speen	28	93.3	47	78.3
Liver	19	63.3	19	31.6
Intestine	13	43.3	14	23.3
Kidney	17	56.6	14	23.3
Gonad	9	30.0	1	1.6
Thyroid	7	23.3	1	1.6
Thymus	17	56.6	5	8.3
Adrenal	16	53.3	4	6.6
Others	8	26.6	7	11.6
Total	191		182	

TABLE 3. Distribution of cleft fetuses according to cleft type (L, lip only; LP, lip and palate; P, palate only), sex, number of visceral anomalies, and number of affected visceral organs.

Cleft Type	*Sex*	*N*	*Number of Visceral Anomalies*	*Number of Affected Organs*
L, LP	M	11	109	66
	F	10	102	65
	?	1	8	5
Subtotal		22	219	136
P	M	3	27	19
	F	4	41	24
	?	1	19	12
Subtotal		8	87	55
Total		30	306	191

TABLE 4. Numbers and percentages of fetuses with various affected visceral organs according to cleft type (L, lip only; LP, lip and palate; P, palate only).

Affected Organ	*L, LP*		*P*		*Total N*
	N	*%age*	*N*	*%age*	
Lung	18	81.8	7	87.5	25
Heart	16	72.7	6	75.0	22
Stomach	7	31.8	3	42.8	10
Spleen	20	90.9	8	100.0	28
Liver	14	63.6	5	62.5	19
Intestine	9	40.9	4	50.0	13
Kidney	13	59.0	4	50.0	17
Gonad	7	31.8	2	25.0	9
Thyroid	5	22.7	2	25.0	7
Thymus	11	50.0	6	75.0	17
Adrenal	11	50.0	5	62.5	16
Others	4	18.1	4	50.0	8
Total	135		56		191

Of 30 cleft specimens, 21 showed external malformations. They were club hands or feet, brachydactyly, syndactyly, polydactyly, malformation or defect of ears or eyes, absence of genitals, no anal opening, skeletal dysplasia, etc. When the group of cleft specimens was divided into two groups according to whether external malformations were present or not, the number of affected organs in each group was significantly different (Table 6). Another significant difference was found between the type of

TABLE 5. Distribution of cleft fetuses according to age, sex, presence of external malformation, number of affected organs, number of anomalies, and cleft type (L, unilateral cleft lip; LL, bilateral cleft lip; LP, unilateral cleft lip and palate; LLP, bilateral cleft lip and palate; Lm, median cleft lip; P, complete cleft of the palate; Pp, posterior cleft of the palate).

Cleft Type	*Specimen*	*Age (weeks)*	*Sex*	*External Malformation*	*Number of Affected Organs*	*Number of Anomalies*
L	X 2448	10	M	yes	5	6
L	X 2464	16	M	yes	8	18
L	J 20	11	M	yes	3	4
L	C 257	16	F	—	7	9
Lm	X 599	15	F	—	3	4
LP	X 3688	13	F	yes	10	18
LL	X 478	16	F	yes	7	10
LL	X 3636	7	?	yes	5	8
LP	X 3196	11	M	yes	7	12
LP	W 85	19	M	yes	7	12
LP	X 3080	11	F	yes	3	3
LP	X 442	18	M	yes	3	4
LP	X 3596	9	F	yes	10	14
LP	X 2812	16	M	—	4	5
LP	X 2336	12	F	yes	7	12
LP	X 2197	9	F	yes	4	7
LP	W 50	9	M	yes	7	13
LLP	X 2462	12	F	—	8	15
LLP	X 498	11	M	yes	8	15
LLP	X 104	11	F	yes	8	13
LLP	X 1795	8	F	yes	6	10
LLP	X 2993	10	M	—	6	7
Subtotal			22	17	136	219
Pp	X 193	18	F	—	8	18
Pp	X 834	17	M	—	5	7
Pp	X 2326	15	F	—	3	3
Pp	I 29	13	M	yes	6	8
Pp	X 158	12	M	yes	8	12
Pp	X 2139	11	F	—	5	7
P	X 2466	9	F	yes	8	13
P	X 2337	9	?	yes	12	19
Subtotal			8	4	55	87
Total			30	21	191	306

cleft and the association of external malformations (77.2% of the lip and lip and palate group had external malformations while 50% of the palate only group had such anomalies). This result was the same as that of the previous report (*3*), although the materials were somewhat different.

When the specimens were grouped according to sex, no significant difference was apparent (Table 3).

TABLE 6. Mean number of visceral anomalies and mean number of affected visceral organs of cleft fetuses according to presence of associated external malformations.

Group	*N*	*Number of Visceral Anomalies*		*Number of Affected Organs*	
		N	*M*	*N*	*M*
Associated external Malformation	20	225	11.2	137	6.8
No associated external malformation	10	81	8.1	54	5.4
Total	30	306		191	

For additional analysis, the cleft fetuses were divided into two groups according to type of cleft: cleft lip with or without cleft palate, and cleft palate alone. Neither a significantly different distribution of the number of affected visceral organs and the number of visceral anomalies nor a significantly apparent organ specificity was found (Tables 3 and 4).

NOTES ON PARTICULAR ANOMALIES. *Lungs.* The frequency of occurrence of bilateral incomplete lobation in the lungs was as high in the cleft group as in the nonclefts, but cases having two lobes in the right lung and no lobation in the left were characteristic of the cleft group. Most of the cases classified as hypoplastic showed irregularity in shape and marked difference in size between the right and the left. However, some of these hypoplastic lungs had unusual lobations, that is, an extra vertical lobation. Another cleft specimen whose right lung was missing had an extremely small left lung with no lobation. Still another cleft specimen had very peculiar horizontal lobations in both lungs, accompanied by an extra horizontal lobation in the left lung (Figure 1). Absence of lobation was not found in the noncleft group. Twelve cases out of 30 clefts and one case out of 60 nonclefts were hypoplastic.

Heart. To best advantage, heart anomalies require study by serial sections but the gross anatomical variations observed in this study merit attention. In two of the cleft cases the heart was unusually small; in one it was well formed (Figure 2), but in the other there was some deformity accompanied by pulmonary stenosis. Severe hypoplasia of the ventricles were apparent in many of the cleft cases. Severe dilation of ventricles was also marked in some of the cleft cases. In one cleft case the heart was completely absent—only the aortic trunk was formed—but other viscera were missing from this specimen.

A number of anomalies occurred in both the cleft and noncleft groups: pulmonary stenosis in five cleft and in four noncleft cases, and atrial enlargement in eight cleft and in nine noncleft specimens. The latter feature was more striking in the cleft group. Bifid apex had similar incidence in both groups.

Stomach. Judged from a morphological standpoint some of the stomachs of the cleft group were deficient in size and developmentally retarded

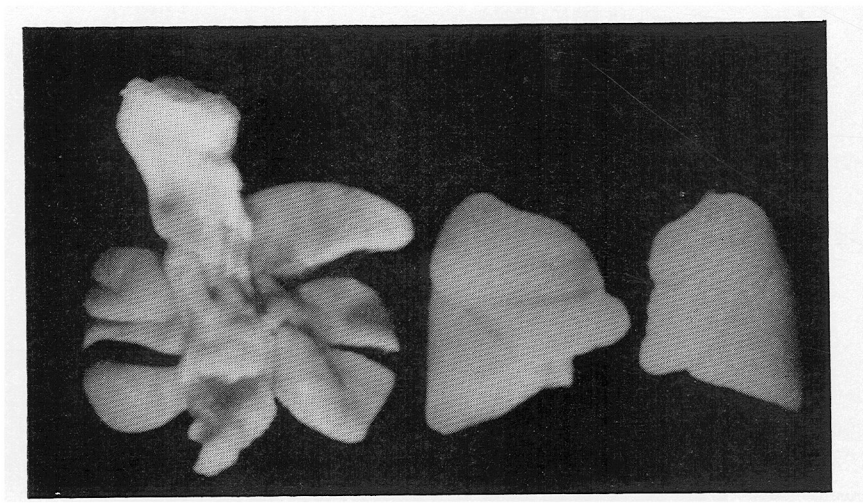

FIGURE 1. Lungs of 11-week-old male fetuses. The lungs of the cleft fetus, on the left, shows an abnormal size and lobation when compared to the normal lung, on the right.

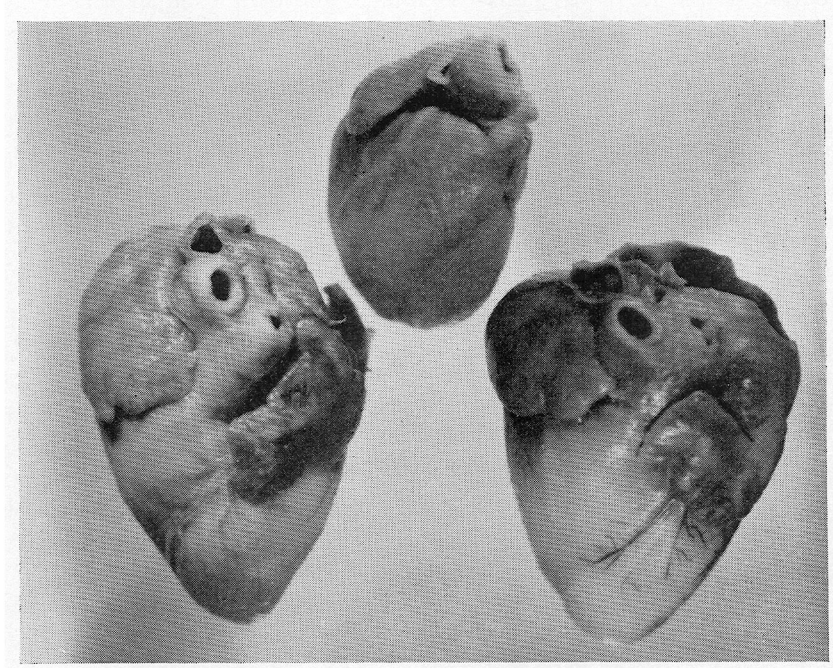

FIGURE 2. Hearts of 18-week-old female fetuses. (upper: cleft; lower: nonclefts) The cleft fetus heart is well-formed, but very small.

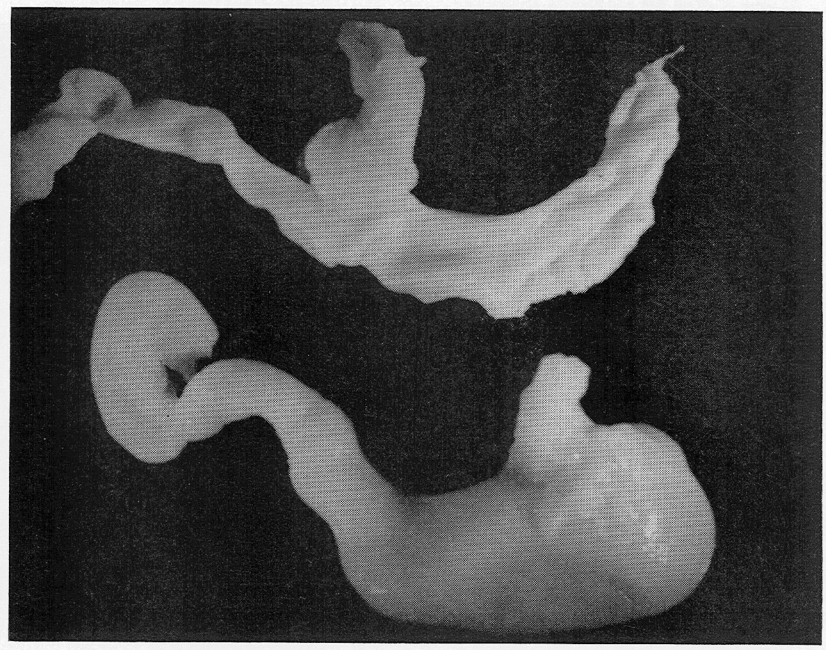

FIGURE 3. Stomachs of 12-week-old female fetuses. (upper: cleft; lower: noncleft) Hypoplastic stomach is shown in the case of the cleft.

(Figure 3); in two cases this retardation was marked, and in yet another case the stomach was absent. Such a degree of abnormality was not found in the noncleft group.

Spleen. Slight partial subdivisions were very common in both cleft and noncleft groups. However, quite frequently, the cleft group showed multiple severe partial subdivisions. These were present in 13 cleft specimens and in four of the 13 the anomaly was accompanied by complete lobation. Complete lobation of the spleen was not found in the noncleft group.

There was some tendency toward enlargement in the noncleft group, but it was most striking in the cleft group. One cleft specimen whose spleen was very enlarged had two attached accessory spleens associated with multiple detached splenic tissue (Figure 4). In two of the noncleft cases the presence of the spleen was questionable, while in three of the cleft cases the spleen was absent.

Liver. Incomplete lobation was frequent in both cleft and noncleft groups. In the cleft group only three cases showed no lobation. In the noncleft group, absence of lobation was also found. In one cleft specimen an abnormal umbilical vein appeared entirely outside the liver. Another cleft specimen had a gross extension of the left lobe due to a defect on the diaphragm (Figure 5). It also showed multiple external lobations in both lobes. Still another cleft specimen had absence of the liver as well as other viscera. In 12 out of 30 cleft specimens the liver was entirely necrotic.

Necrosis was also observed in 10 noncleft fetuses (usually the younger of the group) but the liver was, in general, relatively well preserved in the noncleft group as a whole. In addition many of the cleft specimens showed partial necrosis. This feature was not so striking in the noncleft group.

Intestines. In each of two cleft specimens which had neither cecum nor appendix, the dilated portion between the ileum and the colon was not identifiable. One cleft specimen had abnormally short intestines in which convolutions were absent (Figure 6). There was, however, a tendency to shortness of the intestines of some of the noncleft specimens and, in one, this was associated with an imperforate anus.

Kidneys. Multiple accessory nodules of kidney-like tissue were present in four of the cleft cases; in one of these the right kidney was severely hypoplastic and the left kidney was abnormal in shape and in having two ureters. Much less numerous but larger nodules of accessory tissue were observed in four of the cleft group and in 11 of the noncleft group. One

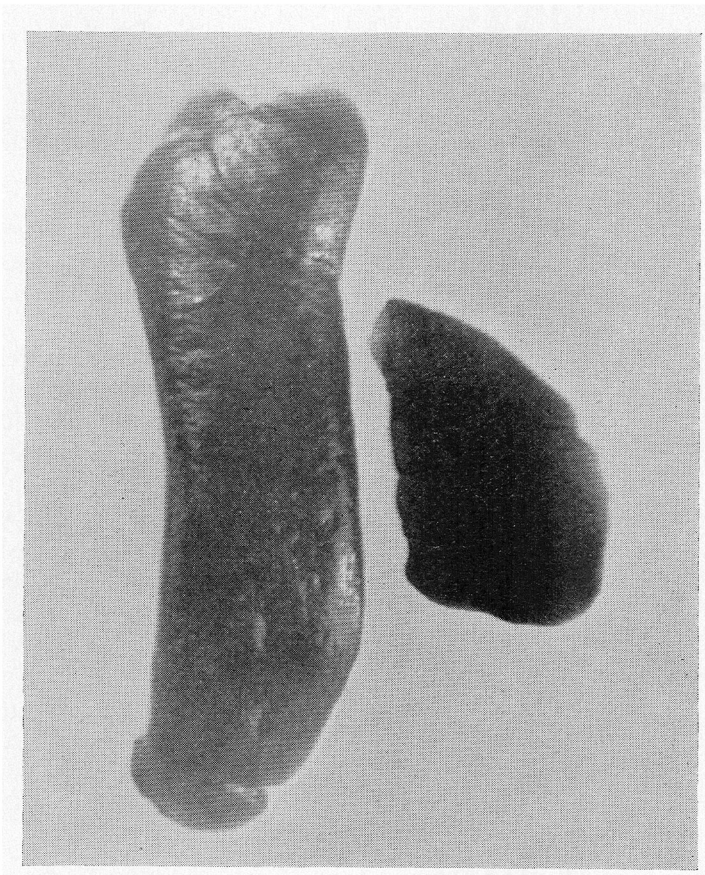

FIGURE 4. Spleens of 11-week-old male fetuses. (left: cleft; right: noncleft) The left specimen shows marked enlargement of the spleen with two attached accessory spleens.

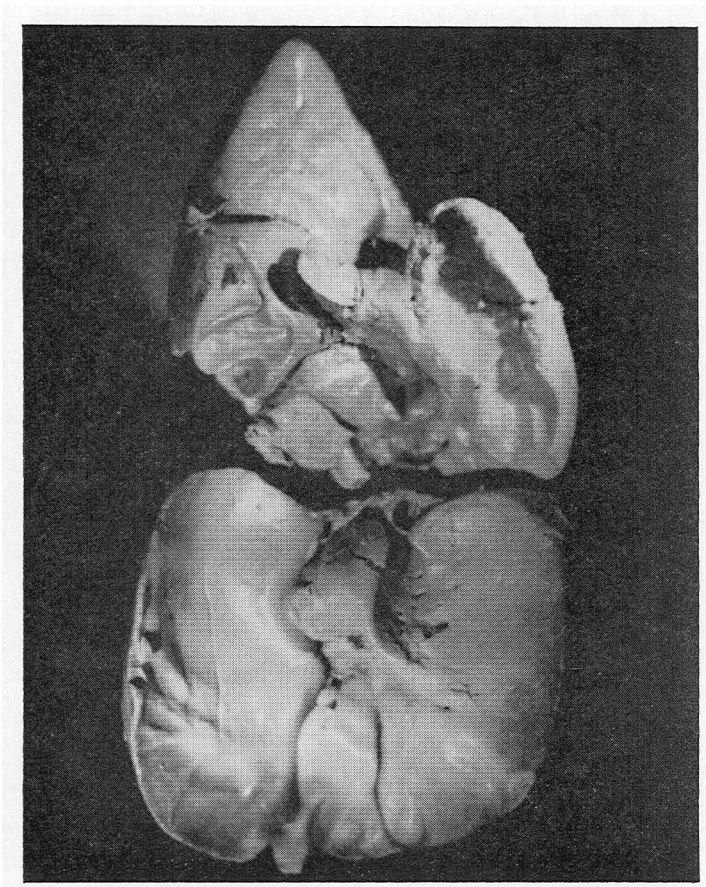

FIGURE 5. Livers of 18-week-old female fetuses. (upper: cleft; lower: noncleft) Dilatation of the right lobe associated with subdivisions of the liver is shown in the case of the cleft.

cleft specimen appeared to have absence of one kidney and the remaining kidney was greatly enlarged. Close to its medial border, however, was a tiny body of kidney-like tissue although no ureter was visible in relation to it (Figure 7). Other conditions found in the cleft group were: one case of severe hyperplasia; one case of polycystosis; two cases of aberrant ureters; one case of complete absence of the kidneys; and two cases of horseshoe kidney. In one of the horseshoe kidney conditions the attachment of the ureters was atypical.

Gonads. A lobed ovary was found in five cleft cases (Figure 8); in three, the condition was bilateral. Absence of the gonads as well as external genitalia was found in one cleft specimen. In the noncleft group there was a case of unilateral agenesis of the gonad.

Thyroid. An aberrant thyroid gland was found in three of the cleft cases. In the first of these the gland was represented by four scattered

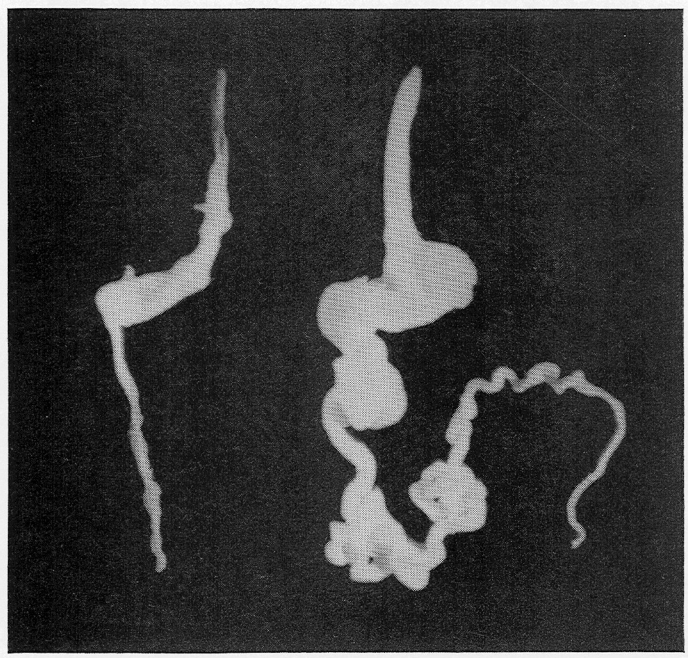

FIGURE 6. Intestines of 9-week-old male fetuses. (left: cleft; right: noncleft) Short intestines with no convolutions and hypoplastic stomach are shown in the case of the cleft.

pieces of thyroid-like tissue; in the second, as a small nodule attached to the sternothyroid muscle; and in the third specimen from which the heart was absent, the thyroid appeared to be only a small nodule located at the side of the trachea. In another two cleft cases, extra thyroid-like tissue was found as a small nodule attached to the sternothyroid muscle.

In still another cleft specimen in which the thyroid appeared to be comparatively normal, two small accessory glands were present in close relation to its inferior margin. Only one abnormal gland was found in the noncleft group. In this case, the thyroid isthmus was absent and both lobes of the gland reduced in size.

Thymus. Ten thymus glands in the cleft group and two in the noncleft group were identified as hypoplastic. In general this took the form of a reduction in size with irregularity in shape, but in two specimens in the cleft group the thymus was represented by aggregations of very small nodules. These were listed as a scattered tissue in Table 7.

The thymus was enlarged in three cleft specimens; in one of them, this was most marked (Figure 9). There was one ectopic thymus in the cleft group, located at the lateral margin of the thyroid gland, and there was one case of absence of the thymus. No marked enlargement was found in

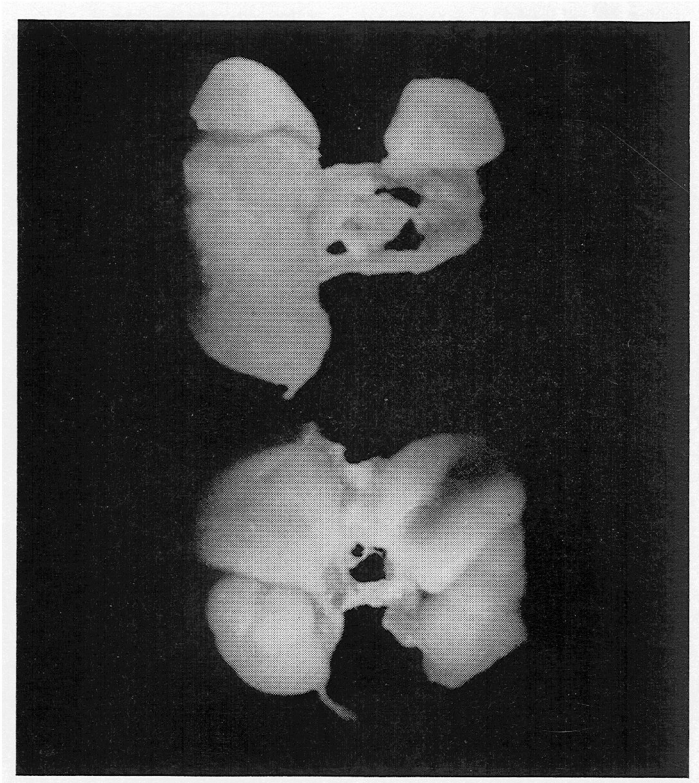

FIGURE 7. Kidneys of 11-week-old male fetuses. (upper: cleft; lower: noncleft) Mono-kidney and hypoplastic adrenals are shown in the case of the cleft.

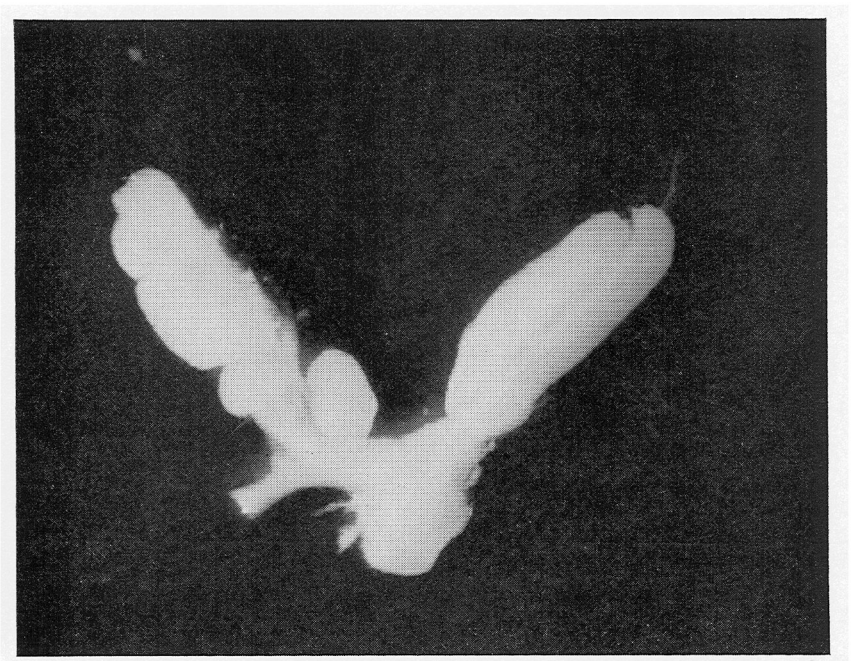

FIGURE 8. Gonads of a 9-week-old female cleft fetus. Lobations of the right ovary are shown.

TABLE 7. Frequency of occurrence of various anomalies in various affected visceral organs of cleft and noncleft fetuses. A bilateral occurrence is listed as two.

Organ	*Type of Anomaly*	*Number of Cleft Group*	*Number in Noncleft Group*
Lung	Incomplete lobation	15	47
	Extra lobation (left)	4	1
	Two lobes (right)	5	1
	No lobation	8	0
	Hypoplasia	12	1
	Ectopia (left)	0	1
	Agenesis (right)	1	0
Total		45	51
Heart	Pointed apex	3	0
	Bifid apex	5	8
	Hypoplastic atrium	10	8
	Hypoplastic ventricle	14	3
	Enlarged atrium	8	9
	Enlarged ventricle	6	1
	Aortic stenosis	4	0
	Pulmonary stenosis	5	4
	Dextrocardia	0	1
	Rotation	1	0
	Agenesis	1	0
Total		57	34
Stomach	Hypoplasia	9	3
	Agenesis	1	0
Total		10	3
Spleen	Slight subdivision	10	40
	Severe subdivision	13	5
	Hypoplasia	5	2
	Accessory	3	0
	Agenesis	3	2
	Enargement	10	2
Total		44	51
Liver	Extra lobation	2	0
	No lobation	3	8
	Dilatation	1	0
	Hypoplasia	1	1
	Aberrant umbilical vein	1	0
	Necrosis	12	10
	Agenesis	1	0
Total		21	19

TABLE 7.—*Continued*

Organ	*Type of Anomaly*	*Number in Cleft Group*	*Number in Noncleft Group*
Intestine	Stenosis of duodenum	1	0
	Stenosis of colon	1	3
	Stenosis of ileum	3	5
	Multiple stenosis	3	0
	Atresia of ileum	1	1
	Atresia of caecum	2	0
	Aplasia of caecum	2	1
	Meckel's diverticulum	4	0
	Diverticulum of colon	2	2
	Shortness	1	4
	Agenesis	1	0
Total		21	16
Kidney	Hypoplasia	3	5
	Hypertrophy	1	0
	Accessory kidney	8	11
	Horseshoe	2	0
	Polycystosis	1	0
	Agenesis	3	0
	Aberrant uretra	2	0
Total		20	16
Gonad	Hypoplasia	6	0
	Lobed ovary	8	0
	Agenesis	2	1
Total		16	1
Thyroid	Ectopia	6	0
	Accessory	4	0
	Hypoplasia	3	1
Total		13	1
Thymus	Hypoplasia	10	2
	Enlargement	3	1
	Accessory	2	4
	Ectopia	1	0
	Agenesis	1	0
	Scattered tissue	2	0
Total		19	7
Adrenal	Hypoplasia	28	4
	Agenesis	2	0
Total		30	4
Others	Umbilical hernia	4	6
	Atresia ani	2	1
	Defect of diaphragm	2	0
	Defect of pericardium	2	0
Total		10	7

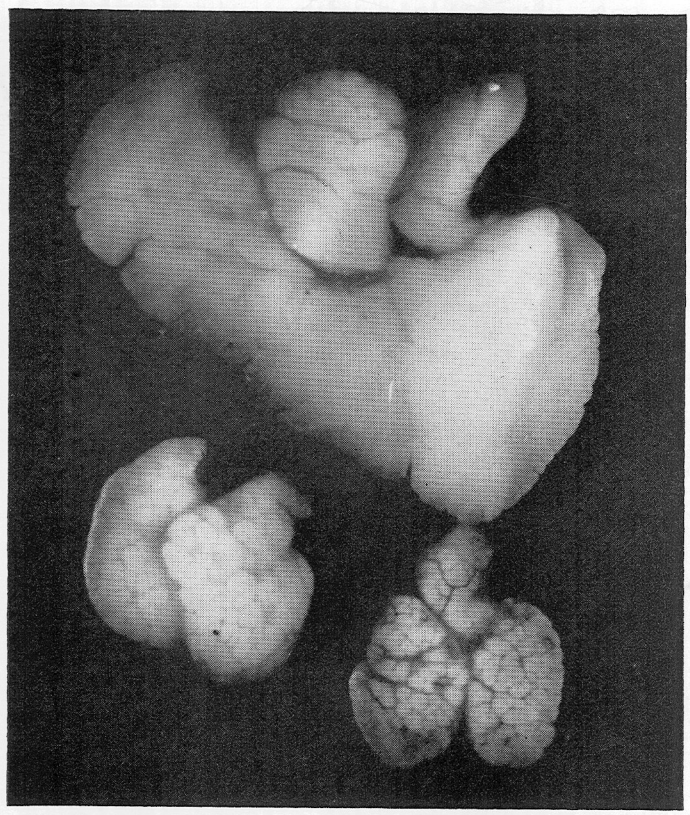

FIGURE 9. Thymuses of 16-week-old male fetuses. (upper: cleft; lower: noncleft) Shown here is a marked enlargement of the thymus of the cleft.

the noncleft group. Accessory thymus had a similar incidence in both the cleft and noncleft groups.

Adrenal glands. Abnormality of the adrenals ranged from unilateral hypoplasia to complete bilateral agenesis. The more severe conditions occurred only in the cleft group. These included 13 cases of bilateral hypoplasia, and one of bilateral renal and adrenal agenesis (Figure 10). Unilateral hypoplasia affected two of the cleft group and four of the noncleft group.

Discussion

It is of interest to note that splenic abnormalities occurring in the cleft group were, in general, more severe than in the noncleft group and that hyperplasia was a characteristic feature of the former group. Willis (*10*) suggested that splenic subdivision is probably due to a deficient circulation resulting from cardiac malformations. Of the 30 cleft palate specimens in this study, 11 cases had severe splenic subdivisions and six of these also had malformation of the heart. This is interesting in view of

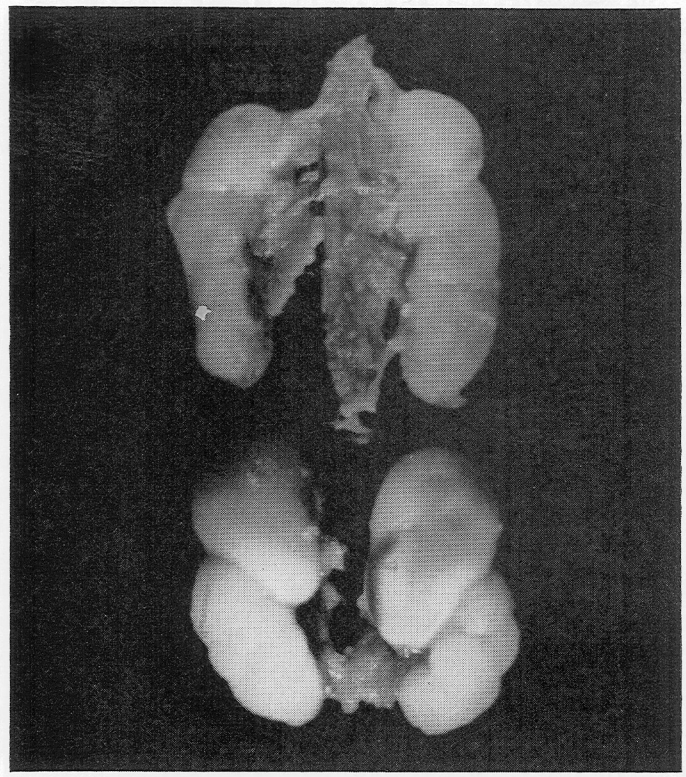

FIGURE 10. Adrenals of 9-week-old female fetuses. (upper: cleft; lower: non-cleft) Hypoplastic adrenals of the cleft are shown.

Sanvenero-Rosselli's (*6*) suggestion that malformations, including cleft palate, may result from defects in the fetal heart.

In this study the liver was entirely necrotic in 12 of the cleft group specimens, and in others of the cleft group there was an appearance in the liver very like that characteristic of localized necrosis.

In relation to the problem of intra-uterine infection, these observations may well be significant. For during fetal life the liver is the first barrier, and the spleen the second, to toxic agencies gaining ingress via the maternal blood. Potter (*5*) suggests that, in the newborn, liver necrosis and splenic enlargement may be due to intra-uterine infections. Potter and Willis both suggest that defects in the fetal heart are probably most frequently due to intra-uterine infections.

It seems unlikely that cardiac or vascular defects are the only primary agents of cleft formation, although heart affliction was more frequent and more markedly severe in the cleft group. It is possible that intra-uterine infection is a factor in the simultaneous production of heart and other visceral anomalies, including lip and palatal defects. Primary lesions in any of the major fetal organs will undoubtedly affect other

structures. Streeter (*8*) suggested that this was probably the case in the association between visceral malformations and external deformity. This correlation was found between external malformations and the incidence of visceral abnormalities in the present study.

Summary and Conclusion

A gross anatomical study was undertaken on the viscera of 30 cleft and 60 noncleft human aborted fetuses, ranging in age from seven to 19 weeks. In general, visceral abnormalities were more frequent and more severe in the cleft specimens than in the noncleft specimens. Certain cardiac defects, hepatic conditions, and splenic and thymic enlargements suggest intra-uterine infection. There was no apparent correlation of type or degree of severity of cleft with type or severity of visceral malformations; likewise, nor was there a correlation found between sex and visceral or palatal defects, although there was a correlation between the presence of associated external malformations and the incidence of visceral anomalies. The high frequency of external and visceral malformations associated with aborted cleft lip and/or palate fetuses suggests the operation of a selective process, permitting only cleft fetuses with attenuated pleiotropic disturbances to survive. It also suggests that cleft lip and/or palate is not just an isolated malformation, as might be concluded from a study of the living, but is part of one or more syndromes affecting visceral and external features alike. It is hazardous to draw any more definite conclusions on the basis of the present study.

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